# Skin
# TUMORS

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## Skin tumors – Part 1



## Skin tumors – Part 2

# Introduction
# Skin tumors (Neoplasms)
# General principles

- **Definition:**

Proliferation of **cells** + CT **stroma** (2 components)

- **Types:**
  1. **Benign**
  2. **Malignant**

     ***Histo-pathological criteria of malignancy:***
     - Atypia (Pleomorphism)
     - Hyperchromatic nuclei
     - Increased nuclear / cytoplasmic ratio

- **Differentiation:**

Degree of **resemblance** of tumors cells to **original tissue** (tissue of origin)
- Highly-differentiated tumors = benign: good prognosis
- Poorly-differentiated tumors = malignant: poor prognosis

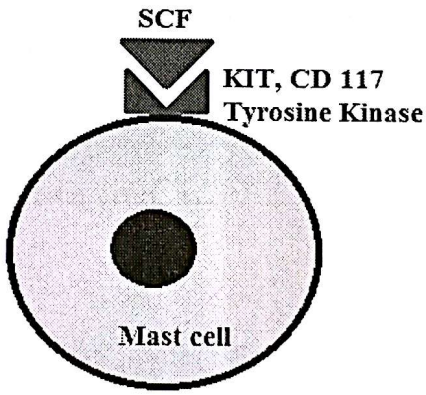
- **Diagnosis (Investigations):**
  1. **Direct:**
     - **Skin biopsy (detection of tumor cells)** مهم جداً
       1. H and E
       2. Special stains
       3. Immunohistochemistry (tumor markers)
     - Genetic (Molecular) study: tumors with genetic base
  2. **Indirect:**
     - Tumor markers in serum, urine, …….etc
  3. **Others: (to detect metastases / systemic affection)**
     - Imaging techniques e.g. CXR, CT, MRI……

# Mastocytosis

- **Definition:**

A **rare** condition characterized by tissue **mast cell hyperplasia** (i.e. increased number) that affects the **skin** (i.e. **cutaneous** mastocytosis) and / or other **organs** (**systemic** mastocytosis) → a **spectrum** of clinical features

- **Mast cells:**
  - Develop in **bone marrow**, circulate in **blood** (in **immature** form), then settle in **tissues** i.e. **CT cells**
  - In the dermis, they are located **near (around) blood vessels** مهم جدا
  - **NO mature mast cells in blood NORMALLY** مهم جدا
  - Mast cells express **(tyrosine kinase, KIT, CD117) receptors** on their surface
  - These receptors are activated by **stem cell factor (SCF)** produced by **fibroblasts** and other CT cells → stimulates cell **growth and survival** (through inhibition of apoptosis)




- **Pathogenesis:**
  - In mastocytosis, there are **auto-activating** مهم **mutations** of KIT receptor genes → **constitutive ligand-independent KIT receptor stimulation** → mast cell proliferation (i.e. mastocytosis)
  - Mast cell **mediators** (e.g. histamine, heparin …..) → **symptoms and signs** of mastocytosis

- **Epidemiology:**
  - **Age**: neonates – adults
  - **Sex**: both
  - **Race**: any

- **Classification:**

*According to age of onset:*
- **Childhood**-onset: before puberty
- **Adulthood**-onset:

*According to system(s) affected:*
- **Cutaneous**: affects the skin only
- **Systemic**: affects multiple organs **(with / without skin مهم جدا)**

*WHO classification:*
- **Cutaneous mastocytosis: (4) مهم**
  1. Urticaria pigmentosa (UP, maculopapular)
  2. Mastocytoma
  3. Telangiesctasia macularis eruptive perstans (TMEP)
  4. Diffuse cutaneous mastocytosis
- **Systemic mastocytosis: ☆☆**
  1. **Indolent** systemic mastocytosis
  2. Systemic mastocytosis with associated clonal hematological non-mast cell-lineage disease (AHNMD)
     Associated with myeloproliferative or myelodysplastic disorder
  3. **Aggressive** systemic mastocytosis
  4. **Mast cell leukemia (MCL)**

- **Clinical picture:**

*Symptoms:*
- May be **asymptomatic**
- Symptoms (if present) are **due to** mast cell mediators (histamine, heparin…..)
- **Cutaneous:** pruritus, urticaria, flushing, **bullae (why??)**
- **Systemic:** (signal the presence of extracutaneous disease)
  - ***GIT:*** epigastric pain, cramping, abdominal pain and diarrhea
  - ***CVS:*** palpitations, dizziness and syncope (vasodilatation)
  - ***CNS:*** headache, problems with mentation (cognitive disorganization)
  - ***Constitutional:*** fever, night sweats, malaise, weight loss
  - ***Bone:*** bone pain

- Relative **absence** of **pulmonary** symptoms in mastocytosis
- **Deaths** associated with extensive mast cell mediator release are **rare**

- Symptoms of mastocytosis can be **exacerbated** مهم جدا by exercise, heat, local trauma to skin lesions, alcohol, narcotics, salicylates and other nonsteroidal anti-inflammatory drugs (NSAIDs), polymyxin B, some systemic anesthetic agents and anticholinergic medications **(importance???)**

*Signs:*

**Cutaneous mastocytosis**

**4 main types** associated with **hyperpigmentation** مهم

**(1) Urticaria pigmentosa (UP)**

- **Most common** in **children** (~65% of childhood-onset mastocytosis) and **adults**
- Variable numbers of tan to brown **macules, patches or papules**
- Most commonly appear on the **trunk and proximal extremities** (less frequently on the face, distal extremities or palms and soles).

**(2) Mastocytoma**

- **Second most common** in **children** (10–35% of childhood-onset mastocytosis) – **extremely rare in adults**
- A **solitary** tan, yellow–tan or brown **plaque or nodule**
- At birth or during infancy – Favor the **distal extremities**

**(3) Telangiectasia macularis eruptiva perstans (TMEP)**

- Extremely **rare both** in children and adults
- Telangiectatic macules / patches without significant hyperpigmentation

**(4) Diffuse cutaneous mastocytosis**

- A form of **childhood** mastocytosis
- numerous erythematous to yellow–tan papules and plaques → confluence → a **leathery texture** (**doughy** consistency – descriptive term: **xanthelasmoidal** mastocytosis)
- Markedly thickened skin with distorted facial features

☆ **Some** infants and children with **UP** and **diffuse** cutaneous mastocytosis develop non-scarring **vesicles or bullae (Bullous mastocytosis** مهم**)**

✓ Result from the release of mast cell serine **proteases** مهم جدا

✓ Usually resolve by 3 to 5 years of age

**Diagnostic signs in cutaneous mastocytosis: (Darier's sign)** مهم جدا

- ✓ Firmly rubbing a characteristic lesion → formation of an urticarial **wheal** at the lesion site (due to release of mast cell mediators)
- ✓ Confirms the presence of mast cell hyperplasia in the skin

| | | **Mast cells concentration** |
|---|---|---|
| Well-demonstrated in | Mastocytomas<br>Childhood UP | **150-fold, 40-fold** greater than normal skin |
| Less apparent in | Adult mastocytosis UP | only **8-fold** greater than normal skin |
| Rarely detectable in | TMEP | |

**Systemic mastocytosis: more common in adults**

- **Bone:** osteoporosis or osteosclerosis
- **BM:** mast cell infiltrate
- **Liver, spleen, LNs:** enlargement (-megaly)
- **GIT:** mast cell infiltrate

**Q Cause of pigmentation in cutaneous mastocytosis:**
**Melanocytes also express KIT receptors**

## • Differential diagnosis:

***DD of UP** (may spontaneously urticate)*

- **Urticaria** (BUT lesions of urticaria last only a few hours and do not have the associated hyperpigmentation seen in UP).

***DD of Bullous mastocytosis: (DD of blisters in children)***

- arthropod bites
- bullous impetigo
- herpes simplex viral infection
- linear IgA bullous dermatosis
- other autoimmune bullous dermatoses
- epidermolysis bullosa
- toxic epidermal necrolysis

***Demonstration of increased mast cells in either the blister fluid or skin biopsy of the mastocytosis patient helps to establish the correct diagnosis.***

***DD of adult mastocytosis:***

- lentigines or melanocytic nevi

***DD of mastocytomas in children:***

- café-au-lait macules, arthropod bites, Spitz or congenital melanocytic nevi, pseudolymphomas and juvenile xanthogranulomas.

- **Diagnosis / Investigations:**

| Direct | Indirect |
|---|---|
| **Biopsy** (skin lesions / internal organs e.g. GIT, BM, …)<br><br>**Skin Biopsy (Histopathology):**<br>***H&E***<br>**Mast cell infiltrate** in the dermis ± eosinophils<br>Mainly in the papillary dermis – **around BVs (why?)**<br>**Large numbers** (mastocytoma, diffuse): **round** cells with **fried-egg appearance** مهم<br>**Small numbers** (UP, TMEP): **spindle-shaped** cells<br>***Special stains:***<br>• **Giemsa** (cytoplasm contains **meta-chromatic granules; blue → purple**) مهم جدا<br>• Toluidine blue<br>• Leder<br>***Immunohistochemistry:*** monoclonal antibodies that recognize **tryptase** or **CD117 (KIT)** | Detection of mast cell **mediators** and/or their metabolites e.g.<br><br>**Serum tryptase** level (>20 ng/ml = systemic mastocytosis)<br><br>**Urine** histamine, histamine metabolites and PGD2 metabolites<br><br>**Plasma** IL-6 |
| **Molecular diagnosis:** detection of KIT gene mutations | |

- **Prognosis:**
  - **Childhood**-onset: frequently **resolves** during late adolescence
  - **Adulthood**-onset: **persists** throughout life

- **Treatment:**

There is **no cure** for this disorder.

Treatment aims mainly at **alleviating symptoms**.

**(1) Reassurance / NO treatment:** if NO symptoms (many patients)

**(2) Avoidance of possible mast cell stimuli (triggers): ????**

**(3) Local treatment**

- Potent and superpotent topical corticosteroids (under occlusion)
- Intralesional corticosteroids

**(4) Systemic treatment**

- Oral H1 and H2 receptor antagonists
- Oral cromolyn sodium (mast cell stabilizer)
- Oral PUVA [psoralens plus ultraviolet A], UVA1
- Oral corticosteroids
- Epinephrine

**(5) Biologic therapy: Imatinib mesylate (KIT inhibitors)** مهم جدا

# Porokeratosis

## Definition:

A ***hyperkeratotic, marginate scaling*** **papule** or **plaque**, with an ***annular*** appearance due to its ***thread-like elevated hyperkeratotic border*** that ***expands centrifugally***

**Nomenclature:**
The disorder was erroneously named porokeratosis because the *column of parakeratosis* known as the *cornoid lamella* was initially described as being present *over a sweat pore*, which of course is a *fixed structure that cannot expand peripherally*

## Aetio-pathogenesis

Although porokeratosis is thought to be a ***disorder of keratinization***, the definitive pathogenesis remains ***unclear***. Therories (باختصار)

1. **(Genetic)** porokeratosis represent an ***expanding mutant clone of keratinocytes***. The characteristic ***cornoid lamella***, seen histologically, represents the ***border between normal epidermis and the mutant clone of cells***.
2. **(Trigger)** A relationship between porokeratosis and ***HPV*** infection
3. **(Immunity)** A ***dermal lymphocytic infiltrate*** *beneath the cornoid lamella* or *in the central zone of the lesion* is considered to be an ***immunologic response*** directed against an ***unidentified epidermal antigen*** (HPV ???) and that this population of inflammatory cells releases ***mediators*** that provide a ***mitotic stimulus*** for ***epidermal cells***

## Clinical Features

### (1) Classic porokeratosis of Mibelli (The *prototype*):

- ***asymptomatic***
- small, brown to skin-colored keratotic **papule** → gradually enlarges over a period of years → a **plaque** several centimeters in diameter. There is a ***raised, sharply demarcated, hyper-keratotic, thready*** **border** with a ***longitudinal furrow***
- **center of the lesion** may be hyperpigmented, hypopigmented, atrophic and/or anhidrotic
- **site:** ***anywhere*** on the body, including ***mucous membranes***, but the **extremities** are most frequently involved

**(2) Disseminated superficial porokeratosis**
**(3) Disseminated superficial actinic porokeratosis (DSAP)**
BOTH:

- small keratotic **papules** (2 - 7 mm in diameter) skin-colored to pink or red in color. As the lesions progress, they expand radially, and the older, **central area** becomes ***atrophic*** while the **well-demarcated border** develops a ***thin, elevated, furrowed keratotic rim***
- Lesions occur in a more ***widespread pattern*** than other types of porokeratosis:
  - Disseminated superficial porokeratosis → ***extremities bilaterally and symmetrically*** sparing the ***palms, soles*** and ***mucous membranes***
  - DSAP → occurs **exclusively** in ***sun-exposed areas***, most commonly the ***legs below the knees***

**(4) Linear porokeratosis**

- one or more **plaques**
- similar in appearance to classic porokeratosis
- follow the ***lines of Blaschko***, most commonly on the ***extremities***

**(5) Punctate porokeratosis = Palmoplantar porokeratosis (of Mantoux)**

- the most difficult type to recognize clinically because of the **small size** of the lesions
- appears during ***adolescence*** or ***adulthood***
- **small (1-2 mm)** ***'seed-like'*** keratotic **papules** with a peripheral raised rim
- on the **palms** and/or **soles**
- **D.D.** It may clinically resemble:
  1. punctate keratoderma
  2. Darier disease
  3. Cowden disease
  4. arsenical keratoses

**(6) Porokeratosis palmaris et plantaris disseminata (PPPD)**

- a **variation** of **punctuate porokeratosis** with lesions *also* present on *other areas of the body*

**(7) Giant porokeratoses:**

- very rare, up to 20 cm in diameter with a surrounding **wall of 1 cm**
- most often found on the **foot**
- Large lesions are said to have the **highest malignant potential**

## Pathology

**Cornoid lamella**

- ***thin column of tightly packed parakeratotic cells*** extending **from** an invagination of the epidermis **through** the adjacent stratum corneum, often **protruding above** the surface of the skin.
  - **Corresponds to** the clinically observed ***raised hyperkeratotic border*** (should be included in the biopsy to establish the diagnosis)
- **Granular layer:** under the cornoid lamella, the ***granular layer*** is either ***absent*** or ***markedly attenuated*** (it is of normal thickness in other areas of the lesion)
- **Spinous layer:** ***dyskeratosis*** and ***pyknotic keratinocytes***
- **The dermis** contains ***lymphocytes*** that may be ***localized beneath the cornoid lamella*** (***lichenoid***)

*** The epidermis in the central portion of the porokeratotic lesion** may be ***normal***, ***hyperplastic*** or ***atrophic***, with ***effacement of rete ridges***

## Differential Diagnosis

1. Other annular lesions (annular erythemas)
2. Actinic keratoses
3. Linear porokeratosis → other linear lesions such as
   - inflammatory linear epidermal nevus
   - incontinentia pigmenti (stage II)
   - linear lichen planus
4. Punctate porokeratosis (**pitted keratolysis, plantar warts**, punctate keratoderma, Darier disease, Cowden disease, arsenical keratoses

None of these lesions have a cornoid lamella. Cornoid lamellae (**column of parakeratosis**) can be found in:

- ***Verruca vulgaris*** (***koilocytosis*** is present with *other histologic features of warts*)
  ***Koilocytes = Large vacuolated cells in the upper epidermis. These cells have a small, dark, hyperchromatic nucleus, surrounded by clear cytoplasm.***
- ***Actinic keratoses*** (but *partial epidermal cytologic atypia* is invariably present)

## Treatment

**Choice of treatment depends on type**

**Localized forms:**

Destruction …

- shave excision
- curettage
- linear excision
- topical 5-fluorouracil (5-FU)
- topical retinoids in combination with 5-FU
- topical imiquimod (Aldara cream)
- Cryotherapy
- $CO_2$, pulsed dye and other **lasers**
- Dermabrasion
- ***Keratolytics***

**Disseminated forms:**

**Systemic retinoids (acitretin)** ****

# Cutaneous Lymphomas

- Cutaneous lymphomas are **lymphoid malignancies** that affect the skin either **primarily** or as **spread** from other organs.
- A cutaneous lymphoma is considered **primary** if "the disease is **limited to the skin** for at least **6 months** after complete staging procedure."
- **Primary** cutaneous lymphomas are either **T or B**-cell lymphomas.
- Primary cutaneous **T-cell lymphomas** represent **more than 80%** of primary cutaneous lymphomas.

## Primary Cutaneous Lymphomas

***WHO-EORTC classification:***
(EORTC, European Organization for Research and Treatment of Cancer).

- Cutaneous **T-cell & NK-cell** lymphomas.
- Cutaneous **B-cell** lymphomas.

### *Primary Cutaneous T-cell (CTCL) & NK-cell Lymphomas*

1. Mycosis fungoides.
2. Mycosis fungoides variants & subtypes:
   - -Folliculotropic MF.
   - -Pagetoid reticulosis.
   - -Granulomatous slack skin.
3. Sezary syndrome.
4. Primary cutaneous CD+30 lymphoproliferative disorders:
   - -Lymphomatoid papulosis.
5. Subcutaneous panniculitis-like T-cell lymphoma.

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### *Primary Cutaneous B-cell Lymphomas (CBCL)*

1. Primary cutaneous **marginal zone** B-cell lymphoma.
2. Primary cutaneous **follicle center** lymphoma.
3. Primary cutaneous **diffuse large** B-cell lymphoma, **leg type**.
4. Primary cutaneous diffuse large B-cell lymphoma, **other**
5. **Intravascular** large B-cell lymphoma.

# 1. Mycosis fungoides (MF)

•Most common type of CTCL, 50% of all primary cutaneous lymphomas

***Etiology:*** The etiology of MF is **unknown**.

**(1) Genetic predisposition**

**(2) Environmental exposure** to **persistent antigenic** stimulation e.g.

- **industrial** chemicals, metals, and pesticides
- **infectious** agents e.g. human T-cell lymphotropic virus (HTLV) I/II, human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human simplex virus (HSV).

**(3) Immunological factors**

- In the **early stages of MF (patch, plaque)**, T cells show a cytokine profile of **Th1** (IFN-γ, IL2, IL12)
- In **advanced stages (tumor)**, a shift in cytokine profile from Th1 to **Th2** with the secretion of cytokines IL4, IL5, IL10

***Pathogenesis:***

•Antigen access to the skin stimulates antigen presenting cells (APCs) in the epidermis such as Langerhans cells (LCs)

•LCs migrate to local skin-draining lymph nodes → T-cell activation → antigen-specific effector/memory cells → circulation → has the ability to home to the original site of inflammation, the skin to combat the antigen (**skin-homing**).

•**Persistent activation of T cells by APCs (LCs)** → clonal dominance, and proliferation of T cells

### ☆ *Mechanism of skin-homing:*

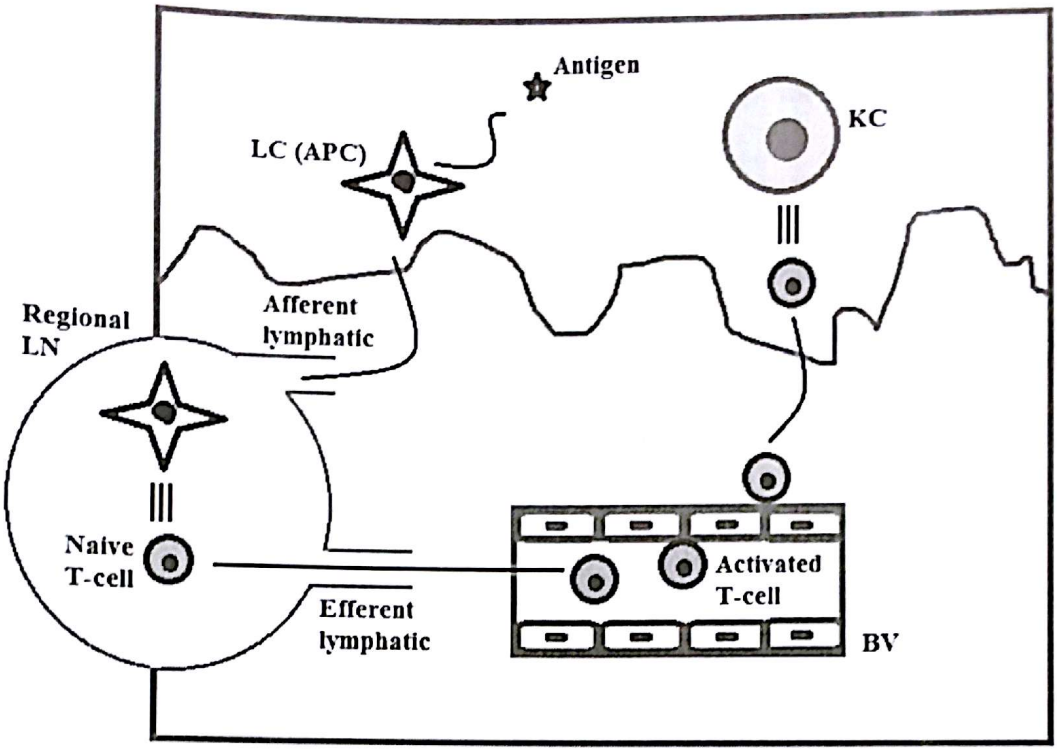
•**rolling/tethering** interactions between T cells and endothelium of capillaries → **diapedesis** → T cells gain entry into the **dermis**

•T cells express certain chemokine receptors such as CXCR3 and CCR4 which have corresponding ligands expressed by keratinocytes → T cells gain entry into the **epidermis** "epidermotropism"

•In early stage of the disease T cells express high levels of chemokine receptors CXCR3 and CCR4 which have corresponding ligands expressed by keratinocytes and LCs, this explains epidermotropism in MF.

•In late stages, the lower expression of chemokines CXCR3 and CCR4 explains the less epidrmotropism.

## Skin-homing or skin-trafficking of activated T-cells




**3 steps related to BVs:**

1. Tethering / Rolling
2. Firm Adhesion
3. Diapedesis (Migration)

***Incidence:*** Rare

***Clinical picture & Histopathology:***

- ☆ Typically affects **older adults (55–60 years)**, but it may occur in **children** and adolescents
- ☆ **Men** are affected more often than women
- ☆ Before a definite diagnosis is made, patients generally have many years of **nonspecific eczematous or psoriasiform skin lesions**.
- ☆ MF passes into **3 stages** (patch, plaque and finally tumor stage)

| Stage | Clinical | Histopathology |
|---|---|---|
| **Patch** | •erythematous, scaly patches<br>•± mildly pruritic<br>•**buttocks** and other **covered sites** of the trunk and limbs (bathing suit)<br>•**poikiloderma atrophicans vasculare (PAV) variant:** patches with mottled hyper- and hypopigmentation, atrophy and telangiectasia | **superficial band-like (lichenoid) infiltrate of atypical lymphocytes**<br>•small to medium-sized, highly convoluted (cerebriform) and hyperchromatic nuclei<br>•few in number<br>•confined to the epidermis (**epidermotropism**)<br>•colonize the basal layer as single cells surrounded by vacuolated halos, in a linear configuration (PAV) |
| **Plaque** | •more infiltrated reddish-brown, scaling plaques<br>•gradually enlarge → annular, polycyclic or typical horseshoe-shaped configuration<br>•**many patients never progress beyond this stage** | •more pronounced epidermo-tropism + dermal infiltrate<br>•intraepidermal nests of atypical cells **(Pautrier's microabscesses)**<br>•epidermis may show acanthosis and elongated rete ridges, but **spongiosis is generally mild or absent** |
| **Tumor** | •nodules or tumors ± ulceration<br>•patients show a combination of patches, plaques and tumors<br>•***If only skin tumors are present without preceding or concurrent patches or plaques, a diagnosis of MF is highly unlikely*** | •the dermal infiltrates involves the entire dermis and extend into the subcutaneous tissue.<br>•**Epidermotropism may no longer be present???** |

***Extra-cutaneous disease:***

- The risk of developing extracutaneous disease correlates with the **extent** and **type** of skin lesions:
  - limited patch/plaque (exceedingly rare)
  - generalized plaques (relatively uncommon)
  - skin tumors or erythroderma (most likely)
- Extracutaneous dissemination, almost without exception, **first involves the regional lymph nodes** draining areas of extensive skin involvement. **Visceral** involvement may develop subsequently and can involve any organ. The **bone marrow is rarely involved.**

***Immunophenotyping:***

**CD3, CD4 positive.**
**CD7, CD8 negative.**

- **Lymphocytes مهم جدا**
  - **B-lymphocytes = CD20 (pan-B marker)**
  - **T-lymphocytes = CD3 (pan-T marker)**
    - **T-helper = CD4**
    - **T-cytotoxic = CD8**

***Immunogenotyping:***

**T-cell receptor gene rearrangement (TCRGR) analysis** using Southern blot or PCR methods

- The TCR is a glycoprotein with four subunits (α, β, γ, and δ).
- In normal peripheral blood T lymphocytes, the TCR genes are composed of 90% to 98% α/β subunits.
- During the process of antigen recognition, the β subunit undergoes TCRGR and, as a result, each T cell produces a singly unique TCR gene.
- A polyclonal population of T cells produces a variety of TCR gene products. In contrast, the T-cell expansion population in CTCL is monoclonal as multiple copies of the same TCRGR are produced by identical daughter cells.

***Diagnosis:***

- Clinical picture
- Histopathology
- Immunophenotyping
- Immunogenotyping

**Staging:** مهم جدا

*TNM staging*

| Classification | Description |
|---|---|
| **T: Skin** | |
| T0 | Lesions clinically and/or histopathologically suggestive of CTCL |
| T1 | Limited plaques, papules, or eczematous patches covering <10% of skin surface |
| T2 | Generalized plaques, papules, or erythematous patches covering ≥10% of skin surface |
| T3 | Cutaneous tumors |
| T4 | Generalized erythroderma |
| **N: Lymph Nodes** | |
| N0 | No palpable lymphadenopathy, lymph node pathology negative for CTCL |
| N1 | Palpable lymphadenopathy; lymph node pathology negative for CTCL |
| N2 | No palpable lymphadenopathy, lymph node pathology positive for CTCL |
| N3 | Palpable lymphadenopathy, lymph node pathology positive for CTCL |
| **M: Viscera (metastases)** | |
| M0 | No visceral organ involvement |
| M1 | Visceral organ involvement, pathology present |
| **B: Blood** | |
| B0 | Atypical circulating cells not present (<5%) |
| B1 | Atypical circulating cells present (≥5%) |

| Stage | T | N | M | |
|---|---|---|---|---|
| **IA** | **1** | **0** | **0** | **EARLY** |
| **IB** | **2** | **0** | **0** | |
| **IIA** | **1–2** | **1** | **0** | |
| IIB | 3 | 0–1 | 0 | |
| **III** | **4** | **0–1** | **0** | مهم |
| IVA | 1–4 | 2–3 | 0 | |
| IVB | 1–4 | 0–3 | 1 | |

***D.D.***

1. **Benign dermatoses (may resemble early MF clinically):**
   - Eczema
   - Psoriasis
   - superficial fungal infections
   - drug reactions

   ***can be excluded by histologic examination***
2. **Other types of (epidermotropic) CTCL, which may resemble MF histologically.**

***Prognosis:***

**Depends on:**

- the stage
- type of skin lesions
- extent of skin lesions
- the presence of extracutaneous disease

**10-year survival rate:**

1. limited patch/plaque stage MF = a similar long-term life expectancy as control population (97%)
2. generalized patch/plaque disease (without LN involvement) (83%)
3. tumor stage disease (without LN involvement) (42%)
4. LN involvement / visceral involvement (20%)

**Cause of death:** systemic involvement or infections.

***Treatment:***

***Early MF (stages IA, IB, IIA):***

**(Skin-directed therapy)**

1. Superpotent topical corticosteroids.
2. Topical chemotherapy.
3. Phototherapy.
4. Electron beam radiation.

•They directly induce apoptosis of malignant cells.

•Topical corticosteroids & PUVA also decrease the number of epidermal LCs and interrupt their chronic stimulation of malignant T cells.

If **clearing is not complete** or patients in stages (IB, IIA), we add a single agent immunomedulator (**Multimodality therapy**):

- IFN-α
- Retinoids: Bexarotene (Targretin) - Acitretin.

***Late MF:***

**Patients with stage IIB:**

1- Multimodality therapy.
2- Single-agent chemotherapy: methotrexate, chlorambucil, etoposide.

**Patients with stage III:**

1- Multimodality therapy.
2- Single-agent chemotherapy.
3- **Extracorporeal photopheresis (ECP).** مهم
The treatment of choice for patients with **erythrodermic MF, SS** and refractory cases. ECP involves the collection of leukocytes by leukapheresis after ingestion of or exposure to 8-MOP. The ex vivo cells are exposed to UV light and then reinfused into the patient.
It results in massive apoptosis of malignant cells.
It induces differentiation of monocytes into DCs capable of phagocytoing and processing the apoptotic tumor cell antigens.

**Patients with stage IV:**

1- Multiagent chemotherapy.
2- Palliative local radiation.
3- Bone marrow/stem cell transplant.

***Multiagent chemotherapy.***

- CHOP (cyclophosphamide, hydroxydoxorubicin, vincristine, and prednisolone).
- EPOCH (etoposide, prednisone, vincristine, doxorubicin, and cyclophosphamide).
- Effective in up to 80% of patients with resistant, extensive or advanced disease.

## 2. Mycosis fungoides variants & subtypes

### Folliculotropic MF (FMF)

- Folliculotropic MF is a variant of mycosis fungoides with distinct clinical and histologic features.
- 10% of MF cases

**Clinical features:**

- **Pruritus** is common in lesions of FMF (more severe than classic MF).
- Lesions often involve the **head and neck** region, with a follicular-based distribution.
- Grouped **follicular papules**, plaques, acneiform-like lesions

**DD:**

- **Scalp:** scarring and non-scarring alopecias
- **Eyebrows:** alopecia mucinosa
- **Face:** comedonal and cystic acne, seborrheic dermatitis and rosacea.
- **Limbs:** AD, keratosis pilaris

**Histopathology:**

- Perivascular and periadnexal infiltrate of T-lymphocytes توصف
- The classic pattern is **folliculotropism** (variable infiltration of follicular epithelium)

**Immunophenotype:** Epidermotropic cells are: عادى

- CD3+, CD4+
- CD8-, CD7-

**Treatment:**

According to the stage as classic MF عادى

## Pagetoid Reticulosis (Woringer-Kolopp disease)

- Pagetoid reticulosis is a variant of CTCL characterized by being **single (unilesional MF)**, affecting the **extremities**, and histologically showing **intense epidermotropism**
- **Rare (1%** of CTCL)

**Clinical features:**

- Single psoriasiform or hyperkeratotic patch plaque
- Affects the extremities
- NEVER extra-cutaneous disease or disease-related death

**Kerton-Goodman type:**

- A generalized form of pagetoid reticulosis.
- Most probably it represents either classic MF, or one of the recently described CTCL.

**Histopathology:**

- **Marked** epidermal hyperplasia with **striking (intense) epidermotropism**.
- The epidermotropic cells are atypical large lymphocytes.
- Some of these cells are CD4+, others are CD8+. أى حاجه

**Treatment: (Single lesion)**

- Surgical excision.
- Local radiotherapy.

## Granulomatous Slack skin (GSS)

Granulomatous slack skin is a very rare form of CTCL. GSS is classified as a subtype of MF with distinct clinical and histologic features.

**Clinical features:**

Circumscribed areas of pendulous asymptomatic skin, mainly in the groins, axillae and abdomen. Initially, indurated plaques often occur which transform into bulky, excessive skin folds.

**Histopathology:**

- Granulomatous infiltrate with giant cells and atypical lymphocytes (hyperchromatic and pleomorphic cells with large cerebriform nuclei), epidermotropism and elastolysis

- The classic pathogenetic concept links the development of hanging skin folds in GSS to destruction of elastic fibers due to elastophagocytosis by giant cells. However, only skin lesions in skin folds such as the axilla and the groin underwent cutis laxa–like changes, whereas skin lesions present at other body sites did not evolve in a similar way.

- These observations suggest that development of hanging skin folds is a location-related phenomenon and not solely the result of the destruction of elastic fibers. Hypothetically, the continuous stretching of elastic fibers in the intertriginous body areas during physiologic movements may facilitate the loss of their function when these regions become affected by lymphomatous infiltrates.

- Granulomatous reaction has been regarded by some authors as a local tissue response to the infiltrating malignant cells or their antigens.

- Genetic alterations with have been reported in a case of GSS, which may indicate genetic predisposition to granuloma formation.

**Treatment:**

As MF, however the excessive **skin folding remains unaffected** with treatment.

## 3. Sezary Syndrome

- Sezary syndrome is a clinical **triad** consisting of erythroderma, peripheral generalized lymphadenopathy and atypical mononuclear cells (Sezary cells).
- ***Rare*** (less than 5% of all CTCL)

**Sezary cells:**

- 5% or more of peripheral blood lymphocytes on a buffy coat smear (B1),
- more than 20% of total lymphocyte count
- 15 – 30% of total WBCs
- a total Sezary count of more than 1000 $\times 10^9$/L (B2).

**Clinical features:**

- Mainly elderly males.
- May develop de novo or as progression from classical MF.
- Intense itching
- Generalized pruritic **erythroderma (erythema and scaling affecting more than 90% of skin surface area)**
- Alopecia
- Ectoropion
- Palmoplanter keratoderma
- Subungual hyperkeratosis

**Histopathology:**

- Similar to MF. (يكتب) عادى

(Extensive dermal – NO epidermotropism)

**Immunophenotype:**

- Large neoplastic cells are:عادى
  CD3+, CD4+
  CD8-, CD7-

**Prognosis:**

- Poor, with a median survival of 35 months
- Most patients die of opportunistic infection

**Treatment:**

- **Extracorporeal photopheresis (drug of choice)** مهم جدا
- Methotrexate
- **Multi-agent chemotherapy:** Chlorambucil + Prednisolone

## 4. Lymphomatoid Papulosis

- Lymphomatoid papulosis is a **chronic recurrent self-healing** eruption of papules and small nodules with the histological features of CTCL.
- Etiology is unknown.
- 10-20% of cases are preceded, concomitant with or followed by another type of lymphoma, usually MF or Hodgkin lymphoma.

**Clinical features:**

- **Age:** Mainly young adults.
- **Sites:** Mainly trunk and proximal extremities.
- **Lesions:** An eruption of reddish brown papules or small nodules. They **erupt and rapidly grow over a few days**. Lesions commonly ulcerate with necrotic centers. **Spontaneous resolution** occurs within a few weeks with atrophic scars. The **cycle recurs** every few months.

**ييجى بسرعه و يروح بسرعه و يرجع بسرعه**

**Histopathology:**

- Three histological subtypes are described:

1- Type A (Histiocytic)

**2- Type B (Mycosis fungoides-like)** **هو ده المهم**

3- Type C (Anaplastic large cell lymphoma-like)☆ ☆☆☆☆

**Immunophenotype:** Large neoplastic cells are:

- **CD30+** ☆☆☆☆☆
- CD3+, CD4+, CD8-

**Immunogenotype:**

- TCRGR showed that atypical CD30+ large cells have a common clonal origin.

**DD**

- Pityriais lichenoides (PLEVA, PLC): younger age, short-lived (no recurrence), no nodules, never or rare malignant lymphoma, CD30+ blast cells are NOT seen
- Folliculitis
- Arthropod bite

**Treatment:**

- As the disease is self-limiting, most patients do not require specific treatment.
- **Systemic therapy:** Systemic steroids – Phototherapy: NB-UVB, PUVA – Methotrexate - Interferon-α2a - Systemic retinoids.

## Subcutaneous Panniculitis-like T-cell Lymphoma

It is a rare form of T-cell lymphoma (less than 1% of all non-Hodgkin's lymphomas). It usually affects young adults, with an equal sex incidence.

**Clinical features:**

- **Age:** Mainly young adults.
- **Sites:** Mainly extremities.
- **Lesions:** Indolent, slowly expanding **subcutaneous nodules**. Occasionally, they may be erythematous, indurated and necrotic.

- Patients may present with systemic symptoms like weight loss, fever, and fatigue due to frequently associated **hemophagocytosis**.
- Dissemination to extracutaneous sites is rare.

**Histopathology:**

- Diffuse cellular infiltrate involving **both septae and lobules** within the subcutis, with relative sparing of the overlying epidermis and dermis.
- The infiltrate is composed of small lymphocytes admixed with large cells having hyperchromatic nuclei.
- The cells show peripheral rimming around fat cells.
- In patients with haemophagocytic syndrome, erythro- and lymphophagocytosis may be present.

**Immunophenotype:**

- Large neoplastic cells are: CD3+, CD4-, CD8+
- In 25% of cases the cells are CD4-, CD8-, CD56+ and express **γ/δ TCR** with **worse prognosis**.

**NB: α/β TCR = good prognosis**

**Treatment:**

- Superficial radiotherapy.
- Chemotherapy.

# Primary Cutaneous B-cell Lymphomas

1. Primary cutaneous **follicle center** cell lymphoma.
2. Primary cutaneous **marginal zone** B-cell lymphoma.
3. Primary cutaneous **diffuse large** B-cell lymphoma, **leg type**.
4. Primary cutaneous diffuse large B-cell lymphoma, **other**
5. **intravascular** large B-cell lymphoma.

## 1. Primary cutaneous follicle center cell lymphoma

An **indolent** primary cutaneous B-cell lymphoma derived from **follicle centre** cells.

**Clinical features:**

- **Age**: adults of both sexes.
- **Sites**: head and neck or trunk.
- **Asymptomatic**
- Solitary or grouped erythematous papules, plaques or tumors.

**Prognosis**: good. If left untreated lesions gradually increase in size, but extra-cutaneous dissemination is uncommon.

**Histopathology:**

- Nodular, diffuse or mixed cellular infiltrate involving the dermis and sometimes the upper parts of subcutaneous tissue.
- The epidermis is not involved.
- The infiltrate may show lymphoid follicles with atypical features;

**Immunophenotype:**

- ☆☆ **CD20+**, CD79a+

**Treatment:**

- Excision of solitary lesions.
- Local radiotherapy.
- Interferon-α.
- ☆☆☆☆**Anti-CD20 antibodies (Rituximab).**
- Systemic chemotherapy.

## 2. Primary cutaneous marginal zone B-cell lymphoma

An indolent cutaneous B-cell lymphoma derived from **post-germinal centre** cells

**Pathogenesis:**

- Association with **Borrelia burgdorferi** infection was reported in areas of acrodermatitis chronica atrophicans.
- Borrelia may produce **chronic antigen stimulation** leading to neoplastic transformation.

**Clinical features:**

- **Age**: young and middle aged adults, with male predominance.
- **Sites**: trunk and extremities are most often involved.
- **Prognosis**: excellent.

Asymptomatic solitary or multiple red to blue-purple dermal papules, plaques or nodules.

**Histopathology:** نفس الكلام

- Nodular or diffuse cellular infiltrate involving the dermis and sometimes the upper parts of subcutaneous tissue.
- The epidermis is not involved.
- Nodular lesions may show reactive follicular structures.

**Immunophenotype:**

- ☆☆ **CD20+**, CD79a+

**Treatment:**

- Excision of solitary lesions.
- Systemic steroids.
- Interferon-α.
- ☆☆☆☆**Anti-CD20 antibodies (Rituximab).**
- Systemic antibiotics.
- Systemic chemotherapy.

### 3. Primary cutaneous diffuse large B-lymphoma, leg type

A malignant lymphoma of **intermediate behavior** characterized by diffuse proliferation of large B cells.

**Clinical features:**

- **Age**: elderly (over 70 years), mainly females (4:1).
- **Sites**: mostly distal part of the leg.
- **Prognosis**: intermediate, relapse is common, extracutaneous spread few years after the onset of disease.

Solitary or clustered erythematous or reddish brown tumors, ulceration is common.

**Histopathology:**

- Diffuse cellular infiltrate involving the dermis.
- The epidermis is not involved.
- The cellular infiltrate is formed of **large cells**, few inflammatory cells and a reactive T-cell infiltrate may be present.
- No germinal centers.
- Prominent mitoses.

**Immunophenotype:**

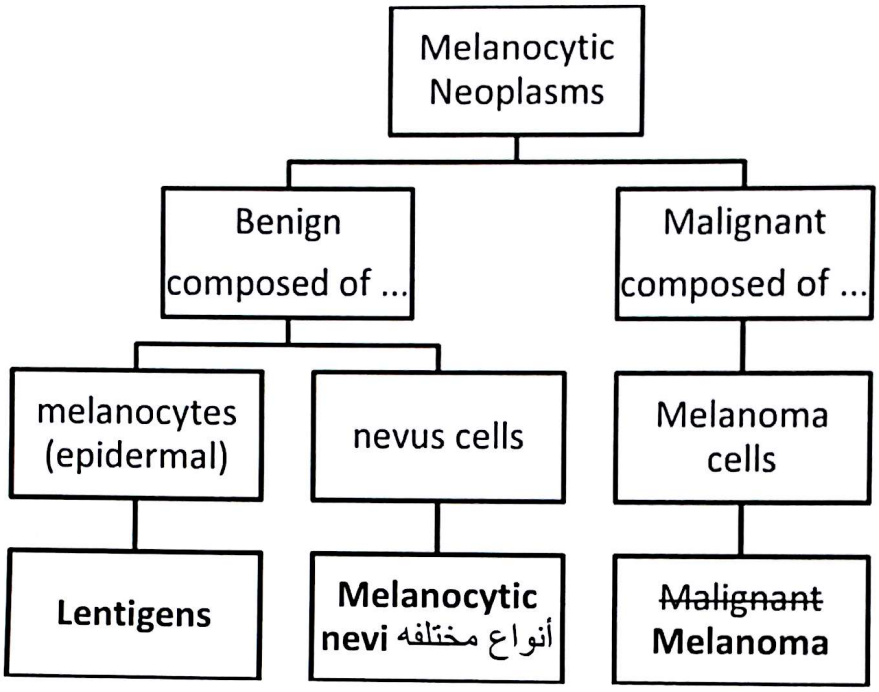
- ☆☆ **CD20+**, CD79a+

**Treatment:**

- Radiotherapy.
- ☆☆☆☆**Anti-CD20 antibodies (Rituximab).**
- Systemic chemotherapy.

# Melanocytic neoplasms

## Classification




**3 types of cells (Histopathology):**

1. **Melanocytes:** solitary dendritic cells
2. **Nevus cells:** cells of melanocytic nevi
3. **Melanoma cells:** cells of malignant melanoma

| Melanocytes | Nevus Cells | Melanoma Cells |
|---|---|---|
| Cytoplasm is dendritic | Rounded or spindle | Rounded or spindle |
| Cells are solitary | Arranged in clusters | In clusters and large sheets |
| Nuclei are small and regular | Nuclei of most cells are small and regular | Most nuclei are large, irregular, and hyperchromatic |
| Mitoses are rare | Mitoses are rare | Mitoses are usually present |

# Melanocytic Neoplasms

## Introduction

## Melanocyte Biology

**Embryology:**

Melanocytes are derived from **neural crest** (neuro-ectodermal) → **migrate** into →

1. the **epidermis** and **hair follicles**
2. the **uveal tract** of the eye (choroid, ciliary body and iris)
3. the **leptomeninges** (arachnoid and pia maters)
4. the inner ear (**cochlea**)

**Clinical significance:** ***genetic disorders of hypopigmentation*** e.g. Vogt–Koyanagi–Harada syndrome, Waardenburg syndrome … etc

- clinically ⇨ leukoderma (vitiligo), congenital deafness, auditory symptoms, heterochromia irides and aseptic meningitis
- aberrant migration/survival of melanocytes

During embryogenesis, melanocytes are found throughout the dermis. By the end of gestation, they migrate into the epidermis

**Clinical significance:** ***Mongolian spot:*** failure of migration of melanocytes from the dermis into the epidermis during fatal life

**Physiology (Melanin formation)**

- ***tyrosinase enzyme*** ⇨ hydroxylation of tyrosine to dihydroxyphenylalanine (dopa) → oxidation → dopa-quinone → polymerized → melanin
- melanin is synthesized and packed in ***melanosomes*** → transferred to KCs via dendrites → located ***supra-nuclear*** (protection against UV)

**Clinical significance:** ***Oculocutaneous albinism (OCA):*** mutations in the ***tyrosinase*** gene ⇨ reduced or absent tyrosinase activity⇨ diffuse pigmentary dilution of the skin, hair follicles and eyes

**Histology:**

***Location:*** wedged between the basal cells of the epidermis

- 1 melanocyte for 5 – 10 basal keratinocytes
- 1 melanocyte for 36 keratinocytes (epidermal melanin units)

*Dendritic cell* ⇨ has dendritic processes (transfer melanin to keratinocytes)

*Special stains:*

1. **Silver** stains (melanin stains **black**) (Fontana-Masson method)
2. **dopa** reaction (**fresh**, unfixed tissue sections incubated in dopa ⇨ staining melanocytes dark **brown** to **black**

*Immunohistochemical detection:*

1. antibodies to **S-100** protein (NON specific also stains Langerhans cells)
2. **HMB-45** antibody (specific)
3. **Melan-A** (high specificity for melanocytes)

## 1. Benign melanocytic neoplasms

## Melanocytic nevi

**Types:**

**a.** Common naevi
**b.** Special naevi
**c.** Dermal naevi

**Naevus** = Latin word for 'maternal impression' or 'birthmark' وحمه

- a circumscribed skin or mucosal lesion
- usually present at / soon after birth
- abnormal mixture of a tissue's **normal** components

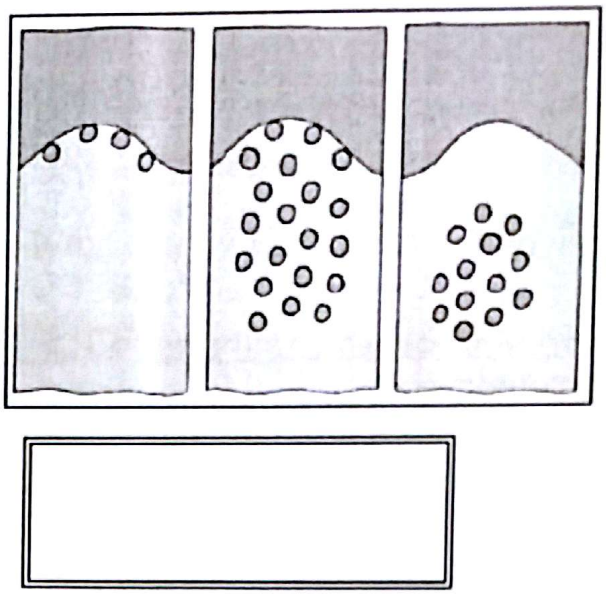
## a. Common naevi

**(Acquired melanocytic naevi, nevo-cellular nevi, moles)**

**Pathogenesis:**

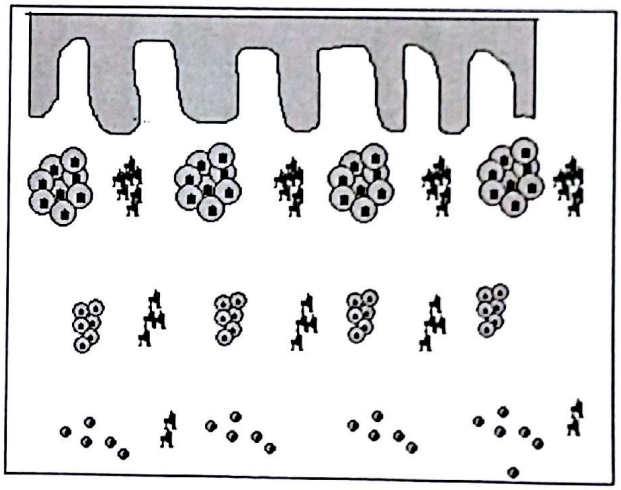
Proliferation of melanocytes at the dermal–epidermal junction ⇨ clusters (**nests**) of melanocytes (***naevus cells***) مهم ⇨

1. all cells remain attached to the basal layer of the epidermis ⇨ **junctional** naevus
2. some cells may migrate into the dermis ⇨ **compound** naevus
3. **The end stage:** no naevus cells are attached to the epidermis + all cells are lying free in the dermis ⇨ (mature) **intradermal** naevus



**Maturation of melanocytic naevi:**

- Melanocytes (naevus cells) proliferate for some time then cease proliferation and differentiate and come to resemble cells of neural or fibroblast lineage



**Histopathology:** when melanocytes goes down (**intra-dermal**) →

1. The cells become ***smaller***,
2. With production of a ***fewer melanin***
3. The ***nests*** become ***smaller and less evident*** (cells are more dispersed)

**Aetiology:**

1. **Genetically**-determined (twin studies)
2. A little effect of **sun exposure** (naevus number is higher in children exposed to more sun)

**Natural history:**

- Develop through childhood
- Naevi continue to erupt in adult life
- After this age, naevi involute (so that the elderly usually have very few)

| | Junctional | Compound | Intradermal |
|---|---|---|---|
| **Clinical:** | Pigmented<br>Not raised (flat) | Pigmented (epidermal component)<br>Raised (dermal component) | Non-pigmented<br>Raised (dermal component) |
| **Histopathology:** | Nests of melanocytes at the ***dermo-epidermal junction*** **only** | Nests of melanocytes at the ***dermo-epidermal junction*** and in the ***dermis*** | Nests of melanocytes in the ***demis*** **only** |
| | | **The dermal cells:**<br>• The more superficial cells **(type A, epithelioid)** as naevus cells, form melanin<br>• The deeper cells **(type B, lymphocytoid)** are smaller and usually contain no melanin – arranged as a band<br>• In the deeper dermis **(type C, spindle)**: cells are arranged as arborizing columns, **spindle**-shaped (resemble cells of **neural** or fibroblast lineage – WHY neural??) | |

**NB. Acquired melanocytic naevi start as junctional anevi which may remain unchanged through much of adult life, or may 'mature' with age, becoming first a 'compound naevus' and then an 'intradermal naevus'.**

**Treatment:**

- No treatment
- Excision (for cosmetic reasons / suspicion of MM) + histopathological evaluation

## b. Special naevi

1. Congenital melanocytic naevi
2. Spitz naevus
3. Halo naevus

### 1. Congenital melanocytic naevi

**Clinical criteria:**

- usually present **at birth**
- may be macular at birth then becomes compound/intradermal (within first few months)
- as the child grows, the naevus **grows** in proportion مهم
- a considerable increase in **terminal hair** (darker and more wiry) especially at scalp
- **giant (garment or bathing-trunk)** naevus
    - very rare
    - common site is the lower back and thigh
    - there may be large numbers of smaller congenital naevi present elsewhere on the infant's skin **(satellite naevi)**

**NB.** in comparison with acquired melanocytic naevi

| Acquired melanocytic naevi | Congenital melanocytic naevi |
|---|---|
| o at childhood | o Since birth |
| o smaller size | o Larger size |
| o stationary and then involute | o ↑ in size with age |
| o lower potential for malignant transformation | o Higher potential for malignant transformation (especially large and giant) |

**Types:** 3 types according to size:

***American National Institutes of Health (NIH) consensus:***

- **small** < 1.5 cm in diameter (very small risk of MM)
- **large** 1.5 – 20 cm (increased risk of MM)
- **giant** ≥ 20 cm diameter (increased risk of MM)

**Histopathological criteria:**

- mostly intra-dermal or compound
- naevus cells extending more deeply into the dermis
- Angio-centric and adnexo-centric (around BVs, adnexa)

  ** **Description of naevus cells (عادى)**

**Complications:**

1. Increased risk of **melanoma** in patients with large naevi (**superficial spreading melanoma** is the most common type)
2. Naevi **over** the **cranium** or **spine** may be associated with leptomeningeal melanocytosis (rarely, complicated by intracerebral primary melanoma)
3. The psychological impact

**Investigations / assessment:**

1. MRI scan
2. Regular neurological examination

⇨ in cases of naevi over the cranium/spine to exclude leptomeningeal melanocytosis

**Treatment:**

***The aims of treatment:***

1. to improve the **cosmetic** effect of naevi
2. to **reduce the risk of malignant transformation**

***Therapeutic modalities:*** (difficult with poor results especially in large / giant naevi)

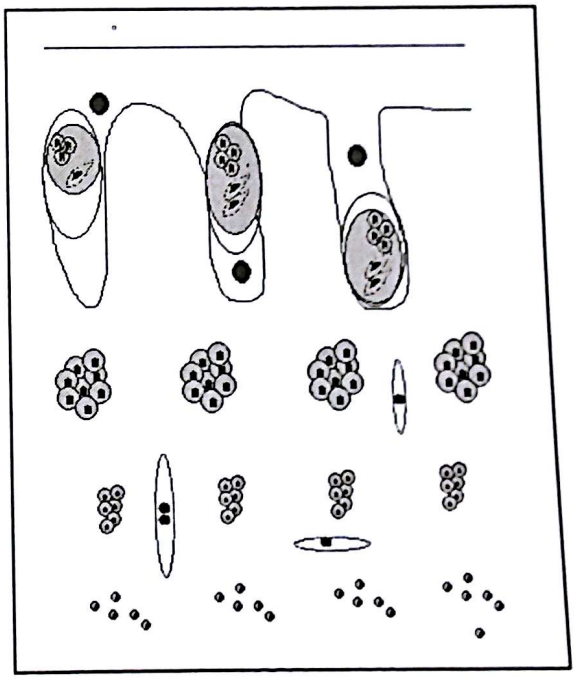
1. surgical (multistep surgery, tissue expanders and grafting)
2. dermabrasion
3. curettage
4. cryotherapy
5. Q-switched ruby laser (694 nm)

## 2. Spitz naevus

First described by ***Sophie Spitz*** → **Spitz naevus / tumor**

**Clinical criteria:**

- Most commonly in **children**
  - were considered as an unusual type of ***melanoma*** → **Juvenile melanoma**
  - Subsequently considered benign → **Benign juvenile melanoma**
- Dome-shaped firm nodule, **red** in colour (dilated BVs - Can be bleached by pressure)
- Most commonly in **head & neck** مهم
- **Grows rapidly** مهم over a period of 3–6 months
- smooth surface



**Histopathological criteria:**

Like **compound** naevus **(2 x 2)**

**(1) Epidermal component:**

► ***Nests of melanocytes at DEJ:***

- Large
- Vertically-oriented مهم
- Surrounded by clefts مهم
- Formed of 2 types of cells:
  - spindle-shaped
  - epithelioid

→ **Spindle and epithelioid cell naevus**

► ***Epidermal changes:***

- Hyperkeratosis
- Acanthosis
- Elongation of rete ridges
- مهم ± ***Kamino bodies*** (degenerating Keratinocytes)

**(2) Dermal component:**

► ***Nests of melanocytes in the dermis:*** حاجات (3) لتحت تنزل ما كل – عادى

► ***Dilated BVs:*** responsible for the red colour of the lesion

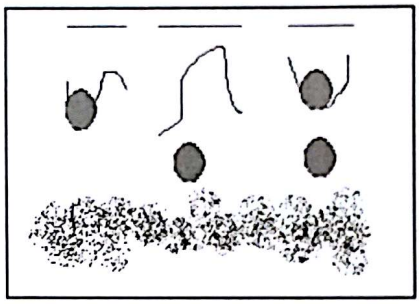
**Differential diagnosis:**

1. **hemangiomas**
2. **pyogenic granuloma**
3. other melanocytic nevi, particularly dermal nevi
4. verrucae
5. molluscum contagiosum
6. juvenile and adult xanthogranulomas
7. dermatofibroma
8. mastocytoma tumors
9. adnexal tumors

**Treatment:**

Surgical excision with a narrow margin of 1–2 mm of normal skin

## 3. Halo naevus (Sutton's naevus)



**Clinically:**

- a pre-existing **melanocytic naevus** أى نوع ⇨ develops a surrounding **halo of hypo-/de-pigmentation**
- The back is the commonest site
- several naevi may develop haloes simultaneously, while other adjacent naevi remain unchanged
- later on (months), the central naevus will gradually disappear leaving a macular area of non-pigmented skin ⇨ may persist for years and may never, or only gradually, return to a normal colour

**Histopathological criteria:**

- Melanocytic naevus عاديه – من أى نوع من الثلاثه
- + ***dense band-like lymphocytic*** infiltrate هو ده اللى عامل المشكله – أهم علامه مميزه
- DOPA stains ⇨ loss of epidermal melanocytes in the halo area

**Pathogenesis:**

- Immunologically-mediated host responses to a naevus
- local and circulating immunological T-cell activation in affected patients
- **Cytotoxic** T-cells → destroy melanocytes
- Associated with MM (melanocytic naevus → halo naevus)

**Treatment:**

1. **Reassurance**
   particularly if the lesions are multiple
   the depigmented areas will burn in sunlight (use a sunscreen)
2. **excision**

## c. Dermal Naevi

1. Mongolian spot
2. Naevus of Ota / Ito
3. Blue naevus

**General characteristics of dermal naevi:**

**Clinically:** *Blue* in colour

- The blue color of the dermal melanocytoses can be explained by **"Tyndall effect"**
- light passing through the skin is scattered as it strikes dark particles, such as melanin
- the colors of light that have a **longer wavelength**, such as red, orange, and yellow, tend to be **less scattered** and therefore continue to travel in a forward direction
- the colors of **shorter wavelength**, such as blue, indigo, and violet, are **scattered** to the side and **backward to the skin surface** (to be seen by inspector eyes)

**Histopathologically:**

- ***Spindle-shaped*** melanocytes ***"immature"***
- Arranged in ***cords*** between collagen bundles & long axes parallel to the epidermis
- Their extruded melanin is engulfed by ***melanophages***
- They differ in the amount of melanin (from minimal to maximum): Ito (minimal) → Ota → Mongolian → Blue (maximum)

### 1. Mongolian spot

Macular blue-grey pigmentation

**Clinically:**

- present at birth in otherwise normal infants
- the patches are rounded or oval in shape, up to 10 cm or so in diameter
- usually single but occasionally multiple
- **Lumbosacral** region is the common site (buttocks, flanks and lower legs)

**Natural history:**

The pigmentation develops in fetal life, increases in depth for a period after birth and then diminishes. It usually disappears during the first decade

**Pathogenesis / Pathology:**

**Treatment:** No treatment is needed

### 2. Naevus of Ota

**Clinically:** = ***oculodermal melanocytosis***

- **unilateral** blue–gray discoloration of the face (mottled or confluent) + involvement of the ipsilateral **sclera**
- favors the distribution of the **first two branches** of the **trigeminal** nerve (ophthalmic – maxillary) ⇨ periorbital area, temple, forehead, malar area, earlobe, pre- and retroauricular regions, nose and conjunctivae
- round, oval or serrated (irregularly demarcated)
- overall size varies from a few centimeters to extensive involvemenet

**Natural history:** Extends over time and **persists lifelong**

**Pathogenesis:**

**Pathology:**

**Treatment:**

Laser therapy (Q-switched ruby, alexandrite and Nd:YAG)

**Naevus of Ito**

As nevus of Ota. Differs only in **distribution** of the ***posterior*** supraclavicular and cutaneous brachii lateralis nerves (supraclavicular, scapular or deltoid regions)

**3. Blue naevus**

**Clinically:**

- well-circumscribed, **dome-shaped papules**, **blue**, blue–gray or blue–black in color (as Spitz but blue) 0.5 to 1.0 cm in diameter
- 50% are found on the **dorsal aspect of the hands and feet** (± other sites)
- Usually, solitary, but may be multiple

**Histopathology:**

- spindle-shaped cells with dendrites (عادى)
- characteristic ⇨ filled with numerous fine melanin granules, often **completely obscuring their nuclei** and extending into their dendrites

**Differential Diagnosis:**

1. **vascular lesions (venous lake and angiokeratoma)**
2. **combined nevus**
3. **glomus tumor**
4. **traumatic tattoo**
5. sclerosing hemangioma
6. primary and metastatic melanoma
7. atypical nevus
8. pigmented spindle cell nevus
9. dermatofibroma
10. papular pigmented basal cell carcinoma
11. apocrine hidrocystoma

**REMEMBER:**

Benign melanocytic naevi (3 x 3) + **Dysplastic** ****

| Common | Special | Dermal |
|---|---|---|
| 1. Junctional<br>2. Compound<br>3. Intra-dermal | 1. Cong. melanocytic<br>2. Spitz<br>3. Halo | 1. Mongolian spot<br>2. Nevus of Ota/Ito<br>3. Blue nevus |

## Other special nevi

## 4. Dysplastic naevus (DN)

- **Clark** et al. (1978) described **families** in which multiple primary melanomas were much more common than expected and who also had large numbers of unusual naevi

**Synonyms**

- Dysplastic melanocytic nevus
- Atypical nevus
- Atypical mole
- Clark's nevus
- B-K mole
- The mole of FAMM (familial atypical multiple-mole melanoma) syndrome
- Nevus with architectural disorder
  The US National Institutes of Health Consensus Conference held in January 1992 recommended that the histologic term "nevus with architectural disorder" **replace** ***dysplastic melanocytic nevus***

- It's a syndrome – 2 schools regarding malignant potential:
  1. High tendency for malignant transformation
  2. Not

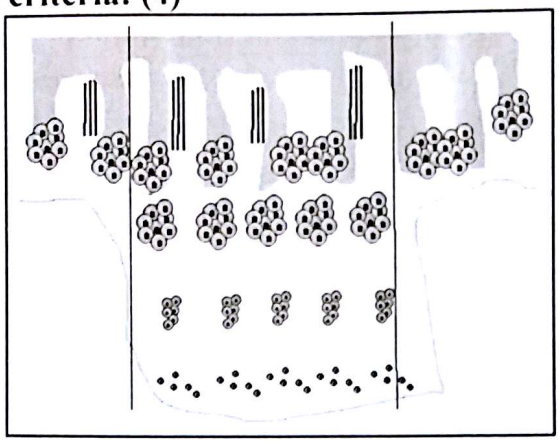
**Clinical criteria:**

- Skin phototypes I & II
- **Center:** compound naevus (raised) – **periphery:** halo of less pigmentation (flat)
- most frequently involve the **trunk** with **predilection** for the **scalp** and for **doubly covered** areas of the body (**breasts** in women and **bathing trunk** area in men).
- Relatively **large number** of nevi

***Morphologic features: ABCDEF***

- **Asymmetry**
- **Borders**: **irregular and ill-defined** borders, but not typically the notched or scalloped borders of melanoma.
- **Coloration**: atypical melanocytic nevi often have **many colors**. They commonly exhibit irregularity of pigmentation with two or three shades of brown, e.g. tan, brown and dark brown.
- **Diameter** (Size): relatively large size ≥ 5 mm
- **Evolution**
- **Funny-looking mole (Ugly-duckling sign**

**Histopathological criteria: (4)**



1. Center → compound naevus + periphery → junctional naevus عادى = ***"shouldering"***
2. Some cells are larger than normal = ***"dysplastic"***
3. Epidermis → acanthosis & elongation of rete ridges – 2 or more nests of melanocytes connect rete ridges together = ***"bridging"***
4. Collagen lamellae in papillary dermis encircle affected rete ***"concentric fibroplasias"*** and/or form stacked layers within dermal papillae ***"lamellar fibroplasias"***

**Treatment**

- There is considerable **variation among physicians** in their clinical approach to patients with DN, which likely stems from different interpretations of the DN and its relative risk of transformation to melanoma.

Atypical nevi are in the majority of cases **benign** stable lesions. They can be **left in place** although the patient must be educated about **monitoring** the appearance of such nevi over time

Where the nevus is sufficiently **atypical** (and particularly when a single nevus is present) then it should be **removed** in its entirety with a **2-mm clinical margin** and subjected to **pathological examination** to exclude in situ melanoma

## 2. Malignant melanocytic neoplasms (Malignant melanoma, MM)

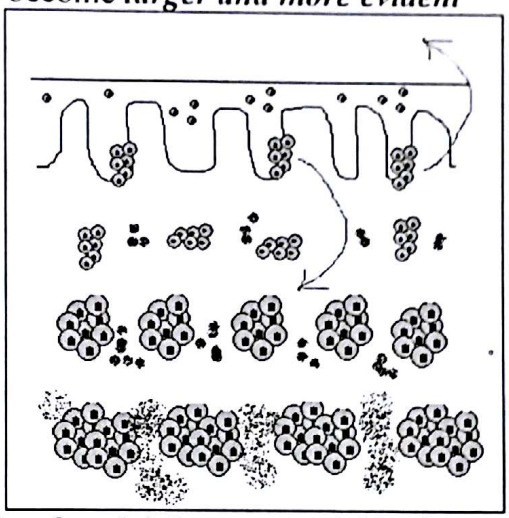
Malignant tumor of melanocytes

**MM in situ:**

- **Clinically:** as junctional naevus (BUT → colour is NOT homogenous "mottled" + larger size + ill-defined margins )
- **Histopathology:** nests of melanocytes at **DEJ & intra-epidermal** (لسه ما نزلتش dermis)

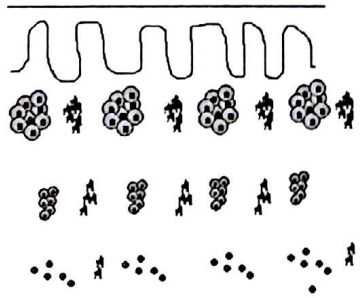
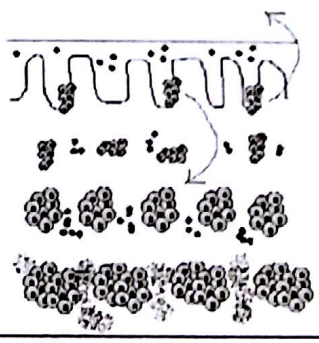
**Behaviour of melanocytes [nests] in MM: مهم جدا**

1. When melanocytes goes up (**intra-epidermal**) → the malignant cells *resist* the *apoptosis* that occurs normally **persistence of large abnormal melanocytes above basal cell layer**
2. When melanocytes goes down (**intra-dermal**) → عكس الطبيعى
   a. The cells become ***larger***,
   b. With production of a ***more melanin***
   c. The ***nests*** become ***larger and more evident***

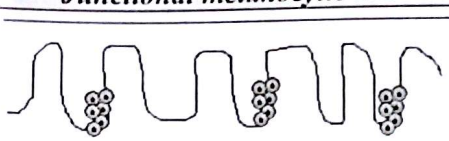
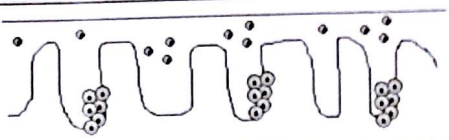


In all cells, there is **atypia** of nuclei (larger + variable sizes and shapes)

**Compare:** (As we go down into dermis ↓↓↓)

| | **Benign naevi** | **MM** |
|---|---|---|
| **Cells** | ↓ in size | ↑ in size |
| **Nests** | ↓ in size | ↑ in size |
| **Melanin** | ↓↓↓ | ↑↑↑ |
| |  |  |

Compare:

| *Junctional melanocytic naevus* | *MM in situ* |
|---|---|
|  |  |
| nests of melanocytes at DEJ only | nests of melanocytes at DEJ + *presence of large abnormal melanocytes above basal cell layer* |

**MM**

**4 types:**

1. **Lentigo maligna:** fair-skinned – sun-exposed parts
2. **Superficial spreading:** trunk
3. **Acro-lentiginous:** extremities
4. **Nodular:** trunk

**2 patterns of growth:**

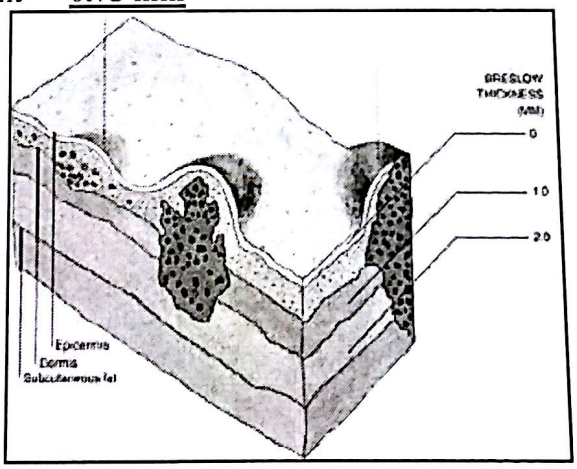
1. **Horizontal (radial):** types 1 & 2 (better prognosis - ↓↓ risk of metastasis)
2. **Vertical:** types 3 & 4 (poor prognosis - ↑↑ risk of metastasis)

**Prognosis** goes worse (from types 1 → 4 : LSAN)

**Commonest types in Egypt:** 3 & 4

**Staging of MM:**

- **Clark "level"**
  - Level I → Confined to the **epidermis** (MIS)
  - Level II → Invasion past basement membrane into the **papillary dermis**
  - Level III → Tumor filling papillary dermis to the **junction** of the **superficial reticular dermis**
  - Level IV → Invasion into the **reticular dermis**
  - Level V → Invasion into the **subcutaneous tissue**
- **Breslow "depth"**
  - Breslow tumor thickness is measured in **mm** from the **top of the granular layer** of the epidermis (or the **base of an ulcer**) to the **deepest point of tumor invasion** using an ocular micrometer.
  - Critical point → **0.75 mm**



## *Risk factors for melanoma*

**GENETIC FACTORS:**

- Family history of cutaneous melanoma
- Lightly pigmented skin (tendency to burn, inability to tan, Red hair color)
- DNA repair defects (e.g. xeroderma pigmentosum)

**ENVIRONMENTAL FACTORS:**

- Sun exposure (Intense intermittent OR chronic)
- Residence in equatorial latitudes
- PUVA
- Tanning bed use
- Iatrogenic or acquired immunosuppression

**BENIGN skin lesions:**

- Melanocytic nevi (multiple, atypical)
- Solar lentigines

**OTHERS:**

- Personal history of cutaneous melanoma

## *Treatment lines of melanoma*

1. Surgery
2. Chemotherapy
3. Radiotherapy
4. Immunotherapy: high-dose recombinant **IL-2**
5. Targeted therapy (Biologics): inhibitors of KIT e.g. **imatinib**
6. Vaccines: **BCG, specific melanoma vaccines**

# Lentigins

**Definition:** multiple hyperpigmented round / oval macules, rarely > 5 mm in diameter

**Classification:**

- **NOT associated with systemic disorders**
  1. Simplex
  2. Senile
  3. Maligna
- **Associated with systemic disorders (Multiple lentigins)**
  1. Localized
     - Peutz–Jeghers syndrome (PJS)
  2. Generalized
     - LEOPARD syndrome
     - LAMB syndrome
     - NAME syndrome

## Lentigo simplex (Simple lentigins)

***Clinical features:***

- light brown to black, homogeneous pigmented macules
- well circumscribed, round or oval, have regular borders, and are usually less than 5 mm (often <3 mm) in diameter
- occurring **anywhere on the body**, including **mucous membranes** and palmoplantar skin
- solitary or multiple lesions
- Frequently found in **darkly pigmented** individuals (BUT **all races** are affected).

***Pathogenesis:***

- An **increased number of melanocytes** within the **basal layer** of the epidermis (**NO Nesting** مهم) → increased production of melanin → hyperpigmented macules

  ?? genetic

  ?? following injury, irritation or PUVA (penile lesions)

  ?? hormonal factors (in women)

*Histopathology*

- **Increased numbers of melanocytes in the basal layer without nest formation**
- **Elongated hyperpigmented rete ridges** ***(dirty feet, dirty fingers)*******
- Increased amount of melanin in BOTH melanocytes and KCs
- Moderate acanthosis (more in mucosal lesions)
- Melanophages and a mild inflammatory infiltrate in the superficial dermis

***Differential diagnosis:***

**Freckles (Ephelides)**

| | **Freckles (Ephelides)** | **Lentigins** |
|---|---|---|
| **Type of patient** | Light pigmentation<br>Red or blond hair<br>Skin phototype I, II | Light/dark (ANY) pigmentation<br>(ANY) Hair color<br>(ANY) |
| **Sites** | Sun-exposed sites (darker in summer, fade in winter and with sun avoidance) | Sun-exposed (solar) and NON sun-exposed<br>Persistent (no effect of sun avoidance) |
| **Clinically** | Light brown, smaller | Dark brown, larger |
| **Histopathology** | Increased melanin<br>NO increase in melanocytes | Increased melanin<br>Increased melanocytes |

**Junctional melanocytic nevus**

- simple lentigo: **absence of distorted skin markings, smaller**
- histopathologic examination may be required for discrimination

**Other types of lentigins (e.g. solar lentigo)**

solar lentigo (larger size, sun-exposed sites)

| | **Melanin** | **Melanocytes** | |
|---|---|---|---|
| | | **Number** | **Nesting** |
| **Freckles** | +++ | **Normal** | **NO** |
| **Lentigins** | +++ | +++ | **NO** |
| **Melanocytic nevus** | +++ | +++ | **YES** |

***Treatment***

- A benign-appearing lentigo simplex: NO treatment
- Suspicious-looking: biopsy to assess for melanocytic atypia
- Generalized: investigations to exclude systemic disease

## Solar (Senile) lentigins
**(liver spots, old age spots, senile freckles)**

*Clinical features:*

- Multiple macules with uniform dark brown colour and irregular outline
- Occur on **sun-exposed** areas (especially dorsa of hands)
- Occur in **fair-skinned old age** (>70 yrs, 90% of Caucasians)
- NO malignant transformation (**BENIGN**)

*Histopathology:*

- As lentigins (عادى)
- + **solar elastosis** in upper dermis
- + MARKED elongation of rete ridges

*Treatment:*

- Cryotherapy, chemical peel (TCA), laser …
- Follow-up for NMSC (chronic sun exposure)

## Lentigo maligna
MM in situ

## Multiple lentigins, Lentiginosis
**Associated with systemic disorders**

- *Localized*
  - **Peutz–Jeghers syndrome (PJS)**
    **Autosomal dominant**
    Lentigines favor perioral region, **oral mucosa** and hands
    Multiple hamartomatous **GI polyps**
    Pancreatic carcinoma; ovarian (adenoma malignum)/testicular tumors
- *Generalized*
  - **LEOPARD syndrome, AD**
    **L**entigines present in infancy/early childhood, **E**CG changes (conduction defects, hypertrophic cardiomyopathy), **O**cular hypertelorism, **P**ulmonary stenosis, **A**bnormal genitalia, Growth **r**etardation, **D**eafness
  - **LAMB syndrome, AD:** Lentigines, Atrial myxoma, Mucocutaneous myxomas, Blue nevi
  - **NAME syndrome, AD:** Nevi, Atrial myxoma, Myxoid mammary fibroadenomas, Ephelides (freckles)

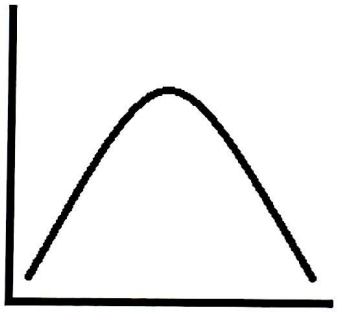
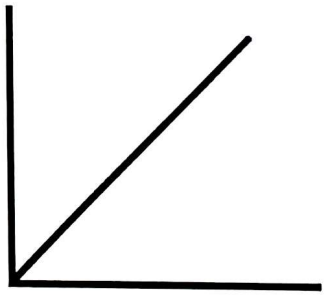
# Vascular tumors

**No agreed classification** ****

1. Vascular birthmarks
2. Cutaneous vascular hyperplasias
3. Distension of pre-existing vessels
4. Benign tumors
5. Malignant tumors

## (1) Vascular birthmarks

2 main categories

| Characteristics | Hemangiomas | Vascular malformations |
|---|---|---|
| **Nature** | **Benign tumors** of vascular endothelium | Congenital structural **anomalies** of BVs |
| **Onset** | First few (3-5) weeks of life (**not at birth**) | Usually evident **at birth** |
| **Course (natural history)** | Grow rapidly, slow growth, involution<br><br>Spontaneous **resolution**<br>  | Persistent growth (proportionate to body growth)<br>**NO spontaneous resolution**<br>  |
| **Sex prevalence** | More in **females** | Female = male |
| **Immunohistochemistry** | GLUT-1 **positive** | GLUT-1 **negative** |
| **Examples** | Infantile hemangiomas | PWS nevus |

# Infantile hemangiomas

- **Definition:** benign tumors of vascular endothelium
- **Incidence:** 4–5% of infants (**the most common tumor of infancy** مهم).
- **Age of onset:** during the first year of life (majority of cases appear within the ***first few (3-5) weeks*** of life).
    - May be present **at birth** (30% of cases) as **red macules/patches****
- **Sex:** more common in ***girls*** than in boys.
- **Risk factors for developing infantile hemangiomas:**
    1. Female infants.
    2. Premature infants.
    3. Low birth weight infants.
    4. Prenatal instrumentation especially chorionic villus sampling.
    5. Multiple gestation pregnancies
    6. Older age of mothers.

## Clinical features:

**Sites: 50%** of cases are located on the **head & neck (anywhere)**
**NUMBER: solitary** (mostly) or multiple

1. **Superficial** hemangiomas (in the **superficial dermis): bright red** in color, **finely lobulated** SURFACE (Strawberry hemangioma)
2. **Deep** hemangiomas (in the **deep dermis** and/or **subcutis)**: warm, **ill-defined**, light **blue**–purple **masses** with **minimal or no overlying skin changes** مهم جدا
3. **Mixed** hemangiomas: have **both superficial and deep** components and present as a well-defineded red vascular plaque overlying a larger, poorly circumscribed light blue nodule.

## Histopathology

Vary according to the ***stage***:
***Location***: superficial, deep, mixed (……)

- ***Proliferative stage:*** well-defined non-encapsulated lobules separated by fibrous septae and formed of **masses of endothelial cells** and pericytes. **Small vascular lumens** may be present focally.
- ***Involuting stage:*** flattening of the endothelial cells, wider lumens and **fibrofatty** tissue.

**Immunohistochemistry:**

- Glucose transporter protein-1 **(GLUT-1) positive** مهم جدا
- Endothelial markers (CD34, Factor VIII related antigen)

**Course:**

- Phase of rapid post-natal growth: 3-6 months
- Slow spontaneous regression:
  **Natural history studies of untreated hemangiomas** demonstrate that **30%** of lesions involute fully by **3 years** of age, **50%** by **5 years**, **70%** by **7 years**, and **over 90%** by **9 years**.

**Complications**

**(1) Ulceration:** The **most common** complication.
**(2) Secondary infection**
**(3) Bleeding.**
**(4) Complications related to large size: High-output congestive heart failure**
**(5) Complications related to location:**

- **Periocular ⇨ astigmatism** (by compressing the globe and deforming the cornea), **visual abnormalities**
- **Pinna: Conductive hearing loss**
- **Anogenital ⇨** ulceration (**painful urination & defecation**)
- **Mouth: feeding**
- **Nose: breathing**
- **Laryngeal:** difficult breathing and stridor.
- **Midline lumbosacral** area: marker for **occult spinal dysraphism**.

**(5) Systemic involvement**

- **Multiple** lesions (small, superficial hemangiomas few millimeters to a few centimeters in diameter, **≥ 5** مهم) may be associated with **visceral hemangiomatosis** (the **liver** is the most common site + other sites)

**(6) Associated syndromes:**
**Kasabach–Merritt Phenomenon (KMP): association** of a ***vascular tumor*** with a ***thrombocytopenic coagulopathy***.

- Vascular tumor: large rapidly growing hemangioma or OTHER tumors
- Blood stasis ⇨ **coagulation** ⇨ consumption of coagulation factors and platelets ⇨ **bleeding** (الاتنين مع بعض)
- **Clinically**: disseminated intravascular coagulation (**DIC**) = generalized petechiae, purpura, bleeding
- **Life-threatening** with high mortality (>30%)
- **Treatment:** corticosteroids + IV heparin followed by (platelet concentrate, fresh frozen plasma, cryoprecipitate)

- **PHACE[S] syndrome** (**P**, posterior fossa and other structural brain malformations; **H**, hemangioma; **A**, arterial anomalies of cervical and cerebral vessels; **C**, cardiac defects (especially coarctation of the aorta); **E**, eye anomalies; **S**, sternal defects and supraumbilical raphe).
- **LUMBAR** syndrome (**L**, lower body/lumbosacral hemangioma and lipomas or other cutaneous anomalies (e.g. "skin tags"); **U**, urogenital anomalies and ulceration; **M**, myelopathy (spinal dysraphism); **B**, bony deformities; **A**, anorectal and arterial anomalies; and **R**, renal anomalies)

## Differential Diagnosis

**Clinical diagnosis** of hemangiomas is usually **straightforward** especially **superficial** and **mixed** types (i.e. hemangiomas with a **superficial component**).

(1) Early Hemangioma (**precursors**): **capillary malformations** (PWS)
(2) **Deep / mixed** hemangiomas: **vascular malformation** (venous, lymphatic or combined)
(3) **Small superficial** hemangiomas: **pyogenic granulomas, Spitz's nevus.**

## Investigations:

To search for systemic affection
To determine exact extension of mixed/deep lesions

- Radiologic evaluation (abdominal ultrasonography, CT and/or MRI)
- Cardiac evaluation (Echocardiogram)
- Ophthalmologic and / or otolaryngologic (laryngoscopy) evaluation

Choice of an investigation is guided by location, extent, associated symptoms and expectations

## Treatment

**Lines of treatment: (combination of >1 line of treatment)**

(1) NO treatment (Non-intervention).
(2) Topical treatment: Corticosteroids, β-blockers (**timolol 0.5%** gel or solution), imiquimod 5% cream
(3) Intralesional corticosteroids.
(4) Systemic therapies: Corticosteroids, β-blockers, Vincristine, Recombinant interferon-α (2a and 2b)
(5) Laser therapy: Pulsed dye laser (PDL), Nd:YAG laser
(6) Surgical treatment.
(7) Treatmet of complications e.g. ulceration.

**Choice of treatment:** Depends on

- **Size**
- **Location**
- Interference with **function** (e.g. airway obstruction, vision)
- Presence or absence of **systemic affection**
- Presence or absence of **ulceration**
- Liability for **healing** with scarring / disfigurement e.g. lip, ear pinna or nasal tip

***NO treatment (Non-intervention):*** for **small** lesions **not interfering with function** (most of cases undergo spontaneous resolution with a good cosmetic outcome).

***Systemic therapy – indications:***

1. Threatened vital **functions** (Vision / Airway).
2. Threatened **life** (High-output cardiac failure).
3. Potential for **disfigurement**: Nasal tip / Lip, especially if crossing the vermilion border / Large rapidly growing lesion, especially on the face.
4. Severe/recalcitrant **ulceration**.

***Systemic β-blockers: Mechanism of action:***

- Vasoconstriction
- Decreased expression of pro-angiogenic factors (e.g. VEGF, bFGF)
- Induction of endothelial cell apoptosis (Hemangioma endothelial cells express β2-adrenergic receptors)

## Vascular malformation

***Criteria:***

1. Usually present at birth
2. Male = female
3. Grow continuously proportionate to body growth
4. NO spontaneous involution
5. Negative GLUT-1

***Definition:***

Structural abnormalities of BVs due to abnormal embryonic development

***Classification:***

According to predominant vessel affected + flow characteristics

| | |
|---|---|
| **Slow-flow** vascular malformation | (1) **Capillary** malformations (CM)<br>(2) **Venous** malformations (VM)<br>~~= Cavernous hemangioma~~ زمان<br>(3) **Lymphatic** malformations (LM) |
| **Fast-flow** vascular malformation | (1) **Arterial** malformations<br>(2) **Arterio-venous** malformations (AVM) |

**Complex-combined** vascular malformations are named depending on the vessels involved e.g. capillary–venous (CVM), capillary–lymphatic (CLM), capillary–lymphatic–venous (CLVM), lymphatic–venous (LVM), capillary–arteriovenous (C-AVM) or lymphatic–arteriovenous (L-AVM) malformations.

## *(1) Port-wine stain (Nevus flammeus)*

- **Definition:** PWS is a **low-flow capillary** malformation.
- **Clinical features**
  - ***Age of onset:*** PWSs typically present **at birth**.
  - ***Lesion:*** well-demarcated **red macules and patches**. **Blanch** completely on pressure
  - ***Site:*** PWSs may occur in **any site.** The **most common** location is the **face, unilateral** مهم (rarely bilateral) in the distribution of the **sensory dermatomes** of the **trigeminal nerve** مهم جدا:
  - ☆ **V1: ophthalmic** region (forehead and upper eyelid)
  - ☆ **V2: maxillary** region
  - ☆ **V3: mandibular** region

**Histopathology:** Widely **dilated, thin-walled capillaries** scattered throughout the upper dermis or the entire reticular dermis. Capillaries are engorged with blood & lined with a **single layer of endothelium**.

**Differential diagnosis**

- Precursor (Patch) lesions of infantile hemangiomas.
- Salmon patch

**Natural history (Course)**

- PWSs **do not involute** spontaneously and **continue to grow** over time (proportionate to the child's growth). Over time, PWSs become **deeper red** in colour, **thicken** and may become **nodular**. Superimposed **pyogenic granulomas** may occasionally appear لازم تتعالج بدرى.

**Complications / Sequelae**

1. **Overgrowth** of **maxilla** and other **facial bones** underlying a PWS
2. Affected **gums** and **lips** may **enlarge** resulting in gingival bleeding, macrocheilia and lip incompetence.
3. A **dorsal midline** PWS (e.g. **lumbosacral** area) may be a hallmark for occult **spinal dysraphism**.
4. **Syndromes** associated with PWS:

***Sturge–Weber syndrome (SWS):*** A **triad** of

1. **Facial CM (PWS):** typically involves the **V1 region** (forehead and upper eyelid) whether unilaterally or bilaterally
2. Ipsilateral **ocular** anomalies: **glaucoma** or **choroidal vascular malformation**.
3. Ipsilateral leptomeningeal / brain (**neurologic**) anomalies: **seizures (epilepsy)**, contralateral hemiparesis or hemiplegia, ....

The combination of **skin**, **eye** and **neurologic** lesions (as in SWS) is referred to as "**phakomatosis**" **مهم جدا. Inherited** disorders.

***Klippel–Trenaunay syndrome (KTS):***

Klippel–Trenaunay syndrome (KTS) is a combination of a **limb CVM or CLVM** with progressive **overgrowth** of the affected extremity.

1. PWS or any other (e.g. AV) malformation
2. Varicose veins
3. Hypertrophy of soft tissue, muscles and bones ⇨ asymmetrical limb enlargement both in length and width (girth)

**Treatment**

- The 2 main lines of treatment are
  - **lasers** (e.g. PDL – **TR of choice**)
  - cosmetic **camouflage** (thick opaque make-up)

## (2) Salmon patch

**Synonyms:** Nevus simplex, Angel's kiss, Stork bite (on the neck)
**Definition:** A very **common** capillary malformation (**40% to 70%** of newborns) resulting from **dilation** of dermal capillaries.
**Clinical features:** Erythematous patches located on the **mid-face** (forehead, glabella, tip of the nose and philtrum), **eyelids**, and **nape** or **occiput** (**central and symmetric – compare PWS مهم جدا**.
Prognosis / course: Salmon patches on the **face fade spontaneously** within 1-3 years, but those on the **nape** may **persist** for life (inconspicuous and covered by hair).

# (2) Cutaneous vascular hyperplasias

## Pyogenic Granuloma

**Synonyms:** Eruptive hemangioma, Lobular capillary hemangioma, Tumor of pregnancy

> ***NB. Pyogenic granuloma is a misnomer. There is no evidence to implicate any infectious agent, and the histologic appearance is not granulomatous.***

**Definition:** benign vascular neoplasm / hyperplasia??

**Epidemiology**

- **Age:** any age (more common in **children** مهم جدا **and young adults**)
- **Sex:** slight **male** predominance
- **NO racial or familial** predisposition

**Pathogenesis:**

- **Reactive** neovascularization (association with a pre-existing **injury / trauma** or irritation in about **1/3 of cases**)
- **Abnormalities** in blood flow (eruption of pyogenic granulomas within pre-existent PWS)

**Clinical features**

- A **solitary** red papule or polyp, **exophytic**, sometimes **pedunculated**,
- Smooth surface that may show ulceration and crustation
- **Grows rapidly** (several weeks or months), stabilizes and then may decrease in size (final size is rarely >1 cm) = *Eruptive hemangioma*
- The **most common sites** (decreasing order of frequency): gingiva, **fingers**, **lips**, face and tongue (Gingival lesions are relatively common during pregnancy = *Tumor of pregnancy, Granuloma gravidarum*)
- Extremely **friable**, frequently **ulcerate** and may **bleed profusely with minor trauma** مهم جدا
- Multiple **satellite lesions** occasionally develop near a primary pyogenic granuloma, usually after destruction of that lesion

**Histopathology**

- **Well-circumscribed**, defined by epidermal "**collarette**"
- Proliferation of small capillaries, arranged in a **lobular pattern** separated by **fibrous septa** (*Lobular capillary hemangioma*).

- Capillaries are lined by flattened to slightly plump endothelial cells, surrounded by pericytes
- Stroma: edematous fibromyxoid interstitial stroma containing fibroblasts.

**Differential diagnosis**
**Glomus tumors, Spitz nevus, hemangiomas**, irritated melanocytic nevi
OTHERS: amelanotic melanoma, bacillary angiomatosis, Kaposi sarcoma

**Treatment**
- Shave excision followed by electrosurgery of the base (local anesthesia with adrenaline) = Possibility of recurrence after removal
- Excision with suturing = LESS recurrence after removal
- Pulsed dye laser
- Sclerotherapy

## Angiolymphoid Hyperplasia with Eosinophilia (AHE)

**Epidemiology**
- **Age:** young to middle-aged adults
- **Sex:** equal

**Pathogenesis**
**Reactive**, rather than neoplastic, process
- Role of **trauma** (history of trauma in some patients)
- Role of **arterio-venous (A-V) shunting** (associated with arteriovenous fistulas and malformations).

**Clinical features**
- ***Lesions:*** Papules or nodules – brown, pink or dull red in color - Multiple lesions, in a **clustered** pattern - Mostly **dermal** in location, but some are subcutaneous
- ***Site:*** mainly in the **head and neck** (especially **around the ears** and on the forehead and scalp) – less commonly: mouth, trunk, distal extremities, vulva and penis.
- ***Symptoms:*** asymptomatic, painful, pruritic or pulsatile
- ***Other findings (may be present):*** regional lymph node enlargement + peripheral **eosinophilia**.

**Histopathology**

- Typical lesions involving the **dermis** and may be subcutaneous tissue
- **Well circumscribed**
- Proliferations of capillary-sized **vessels** = lined by **enlarged endothelial cells that protrude into the lumen**, producing a scalloped or "**cobblestone**" appearance.
- Surrounding dense perivascular inflammatory infiltrate (**lymphocytes** and **eosinophils**)

**Differential diagnosis**

- **Pseudo-lymphoma**
- **Sarcoidosis**
- **Angiosarcoma**
- **Metastatic tumors مهم (vascularized)**
- **Kimura's disease مهم:** Kimura's disease is a distinct entity (much larger lymphoid follicles – usually located on the posterior neck)

**Treatment**

- Surgical excision (one-third of lesions recur)
- Lasers (e.g. CO2, pulsed dye)
- Sclerotherapy (for the deep vascular component)

**Angio-** = proliferation of BVs + plump endothelial cells
**-lymphoid** = increased lymphocytes
**Eosinophilia** = increased eosinophils

# (3) Distension of pre-existing vessels

## Angiokeratomas

**Definition:** superficial (papillary dermis) ***vascular ectasia*** + ***hyperkeratosis***

**Five clinical variants:**

**(1) Angiokeratoma of Mibelli (classic type)**

- Children and young adults (10 - 15 years)
- most commonly on the **dorsal** and lateral aspects of the **fingers** and **toes**, dorsa of the **hands and feet** (rarely on the elbows and knees)
- **multiple, bilateral and symmetrical**
- minute bright red macules that increase in size, becomes elevated **warty** with dark color – may be associated with chilblains and acrocyanosis
- familial predisposition (may be transmitted as AD)

**(2) Angiokeratomas of the scrotum / vulva (Angiokeratoma of Fordyce)**

- Along superficial vessels
- Arise in the second or third decade (mostly in older age groups)
- Red-purple to black in color, single or multiple
- may be associated with thrombophlebitis, **varicoceles**, inguinal hernias
- **Vulvar** lesions may be associated with vulvar varicosities, hemorrhoids, **oral contraceptive use**, or increased venous pressure during **pregnancy**

**(3) Solitary angiokeratoma:**

- Blue-**black** small warty papule
- Any site, most commonly **lower limbs**

**(4) Angiokeratoma circumscriptum**

- develops during infancy or childhood
- a **plaque** of multiple discrete papules / hyperkeratotic papules and nodules that become confluent
- affecting **trunk**, arms or legs, **unilateral** in most patients
- **female** predominance

**(5) Angiokeratoma corporis diffusum**

A part of clinical manifestations of …

***Fabry disease***

- **X-linked recessive**
- deficiency of the **lysosomal enzyme α-galactosidase A**
- accumulation of the neutral **glycolipid ceramide trihexidose** within lysosomes of multiple cell types
- **Skin** lesions:
- multiple, clustered **angiokeratomas**, usually in a **bathing trunk** distribution (few to numerous) – begin to appear during **late childhood or adolescence** + Dry skin & anhidrosis
- **Systemic** manifestations
    - **Eye** affection e.g. corneal opacity
    - Paraethesia, HTN, renal …
- **Cause of death:** organ failure (renal, cardiac) – cerebro-vascular stroke

**NB. Angiokeratoma corporis diffusum occurs in other deficiencies e.g. fucosiduosis and galactosidosis**

**DD: according to type**

- Solitary: melanoma
- Angiokeratomas of Fordyce: genital warts
- Angiokeratoma circumscriptum: lymphangioma circumscriptum

**Pathology**

- ***Epidermis:*** acanthotic, hyperkeratotic, elongated rete ridges
- ***Papillary dermis:*** marked dilatation of BVs engorged with blood

**Treatment**

**Removal** for cosmetic reasons (shave excision, diathermy or laser therapy)

## Lymphangiomas (Lymphangiectasias)

- Inaccurate terms
- ***Malformations of lymphatic vessels*** (cutaneous, SC, sub-mucosal)
- 3 main types: superficial & deep & mixed

**(1) Superficial lymphatic malformation**

= Lymphangioma circumscriptum اسم خاطى لكن مشهور

= **Micro**-cystic lymphatic malformation اسم ادق

- **Most common** type of lymphatic malformation
- Appears **at birth or shortly after**
- Single/multiple patches of **tense grouped translucent vesicles (frog spawn),** When punctured, **clear colourless fluid** مهم جدا فى التشخيص
- Later, may become **verrucous** and brown (DD: wart)
- Affects any site: axilla, shoulder, neck, **trunk**, proximal limbs, tongue
- Histopathology: **Dilated lymphatic vesels** in the **superficial** (papillary) dermis filled with lymph (**pale pink**). Overlying epidermis: atrophic (early) – hyperkeratosis, acanthosis (late)

**(2) Deep lymphatic malformation**

= Cystic hygroma اسم خاطى لكن مشهور

= **Macro**-cystic lymphatic malformation اسم ادق

- Soft circumscribed SC swelling
- Overlying skin is normal مهم جدا
- Neck ***, axilla, groin
- Histopathology: as superficial BUT larger in size and deeper (SC tissue)

***Treatment of all types: Surgical excision, CO2 laser (recurrence)***

## Miscellaneous

**Cherry angiomas, Senile angiomas, De Morgan spots**

- 1-5 mm red to purple papules
- On the **trunk** + upper extremities
- Vey common
- Middle-aged and **elderly** people (senile)

**Spider nevus, nevus araneus, spider telangiectasia**

- Most common form of telangiectasia
- ***Central slightly-elevated red punctum + fine BVs radiating form it***
- Face and **upper chest**
- Associated with **LCF + pregnancy**
- **PDL** is the treatment of choice

**Venous lake**

- Small dark blue elevated soft lesions
- Mainly on **lips** + other sites
- Compression ⇨ emptied from blood
- TR: laser, electrocautery

# (4) Benign tumors
# Glomus tumors

Benign tumor characterize by the presence of glomus cells
2 main variants:

| | Solitary | Multiple (glomangiomas) |
|---|---|---|
| **Incidence** | More common | Less common |
| **Site** | Acral extremities: nail bed of fingers and toes | Localized in one area or generalized |
| **Symptoms** | Paroxysmal pain | Painless |
| **Age** | Young adults | Children |
| **Sex** | Equal (males mare prone to subungual lesions | Equal |
| **Lesions** | Small purple tender nodule | Multiple |
| **Inheritance** | None | May be AD |

| | Solitary | Multiple (glomangiomas) |
|---|---|---|
| **Histo-pathology** | Well-**circumscribed, capsulated** dermal mass | **NOT capsulated** |
| | Several narrow **vascular lumina** lined with a single layer of endothelial cells | More numerous **vascular lumina** lined with…… |
| | Surrounded by multiple layers of **glomus cells** (round epithelioid, faint eosinophilic cytoplasm, large oval nuclei) | Fewer number of **glomus cells** |
| | **Cells > vascular spaces** | **vascular spaces > Cells** |
| **Treatment** | Surgical excision<br>Electrocautery<br>Sclerotherapy<br>**Lasers (PDL, NdYAg, KTP)** | ~~**Difficult**~~<br>~~**Better Avoided**~~<br>~~**Less effective**~~<br>**Lasers (PDL, NdYAg, KTP)** |

**Glomus cells:**

- **Modified smooth muscle cells**
- Located at specialized **A-V shunts (Sucquet-Hoyer canal)*** ** present at acral sites especially fingertips (responsible for temperature regulation)

**Origin of glomus tumor:**

(1) Glomus cells **at A-V shunts** (**cutaneous** glomus tumor)
(2) **Ectopic** glomus cells (**extra- cutaneous** glomus tumor e.g. GIT, Bone..)
Undifferentiated perivascular cells with the ability to transform into glomus cells

**Immunohistochemistry: Demin +Ve** (like smooth muscles)

***Painful skin tumors:***

Leiomyoma
Eccrine spiradenoma
Neuroma
~~Dermatofibroma~~
Angiolipoma
Neurilemmoma
Endometrioma
Glomus tumor, solitary
Granular cell tumor

# (5) Malignant tumors

## Kaposi's sarcoma (KS)

**Multiple idiopathic hemorrhagic sarcoma**

- **Definition:** rare **multi-focal** vascular neoplasm that affects the **skin** and **other organs**
- **Epidemiology:** According to type

**Aetiopathogenesis:** KS may be due to **viral infections** مهم جدا mainly
- **Human herpes virus 8 (HHV-8)** مهم جدا
- Cytomegalovirus (CMV)
- Human papilloma virus 18 (HPV)

**Clinical types: 4 main types**
**(1)** Classic
**(2)** Endemic (African)
**(3)** Epidemic (HIV-associated)
**(4)** Iatrogenic (immunosuppression-associated)

### [1] Classic KS

- Age: **elderly** (50-80 yrs) مهم جدا
- Sex: **males** (15:1) مهم جدا
- Race: east Europe, Mediterranean, Ashkenazi Jews

***Cutaneous:***
- Bluish red, dark brown papules nodules and plaques
- May be hyperkeratotic / verrucous surface
- Affecting **distal parts of the lower limbs** مهم جدا
- **3 stages: patch, plaque, nodule (tumor)** مهم جدا
- Complications: ulceration, hemorrhage, scarring and lymphedema of affected limb

***Extra-cutaneous: (10% of cases)***
- LN+++ (10%), **Asymptomatic** مهم جدا
- Common sites: **GIT** (abdominal pain and bleeding) – liver – lung – abdominal LNs – heart
- Prognosis: **death** may occur in 10% of cases within 10 yrs (GIT hemorrhage, extensive skin lesion with ulceration, lymphoma)

## [2] Endemic Africans KS

- Age: **adults** (some forms in children)
- Sex: **males**
- Race: equatorial African blacks
- 4 variants
  - Benign nodular: like nodular stage of classic KS
  - Aggressive
  - Florid
  - Lymphadenopathic (more in children, extensive SC LN++, internal organs, minimal skin lesions, aggressive, fatal within 2-3 yrs)

## [3] Epidemic (AIDS-related) KS

**Strong association: AIDS + homosexuality + KS** مهم جدا

- 30 – 40 % of AIDS patients
  - 21% homo-sexual males (from infected male)
  - 4% hetero-sexual males (from infected female)
- **AIDS** is usually of **advanced stage (CD4 count <400 / mm3)**
- **95% of AIDS-KS are homosexual**

**Clinical features:**

***Skin:***

- **Bilateral and symmetrical** مهم جدا
- Smaller in size
- Extensive
- More aggressive / rapid progression
- **Face and upper trunk (nose tip: predilection site)** مهم جدا

***MMs:***

**Oral** mucosa may be 1st site affected (**hard palate**) مهم جدا

***LNs + internal organs***

**Death** due to AIDS-associated **opportunistic infections** (NOT KS itself)

## [4] Iatrogenic (immunosuppression-associated) KS

Prolonged mmunosuppression e.g. after **organ transplants** especially **renal**

Can **resolve upon discontinuation** of mmunosuppressive drugs

**Histopathology:**
Same in all 4 types / **varies** according to the **stage** مهم جدا
***Patch stage: Upper dermis shows***

- **Vascular proliferations**
  - Small and delicate
  - Separated by collagen bundles
  - Lined by few endothelial cells
  - Surround pre-existing BVs / adnexal structures ⇨ seem floating within the newly-formed BVs **(promontory sign)** مهم جدا
- **Sparse infiltrate** (plasma cells, lymphocytes)

***Plaque stage: whole dermis, may be SC tissue***

- Increased vascular proliferations
- **Spindle-shaped cells** with pink cytoplasm

***Nodule / tumor stage***

- **Increased Spindle-shaped cells** (replace dermal collagen, intersecting fascicles separated by **vascular slits** مهم جدا)
- RBCs extravasation, hemosiderin + siderophages

***In brief, vascular proliferations + spindle-shaped cells*** مهم جدا

**Treatment:** According to extent of involvement:

- **Local therapies:**
  - Cryotherapy, radiotherapy, intra-lesional (chemotherapy, sclerosing agents)
  - Surgical excision (small lesions), lasers (PDL, CO2)
- **Systemic therapies:**
  - Chemotherapy: vincristien, bleomycine
  - Immunosuppressives
- **Anti-retroviral therapy for HIV-associated KS** مهم جدا

# Angiosarcoma

- **Uncommon** malignant vascular tumor
- **Endothelial** cell origin (malignant endothelial sarcoma)
- **3 types:**
  **(1)** Angiosarcoma of the scalp and face of the elderly
  **(2)** Angiosarcoma in lymphedema (lymphangiosarcoma)
  After radical mastectomy in ipsilateral arm
  **(3)** Angiosarcoma following radiotherapy (high doses)

# Pseudo-KS
# Acroangiodermatitis of Mali

**Clinically:**
- Pigmented purpuric eruption affecting skin around malleoli / dorsa of feet
- Brown papules ⇨ plaques (similar to KS)

**Causes:** 5 possible causes
1. Chronic venous HTN (varicosities)·
2. A-V malfromations
3. Iatrogenic A-V shunts (CRF on dialysis)
4. Amputated limb
5. Paralyzed limb

**Histopathology:**
- **Benign** كلمه مهمه جدا capillary proliferations with plump endothelium
- **NO spindle cell proliferation** مهم جدا
- Extravasation of RBCs

**Clinical DD**
- KS
- Gravitational eczema
- Schamberg's disease (PPD)

**Treatment:**
- Of the underlying **cause**
- Vascular support (elastic stockings)

**Histopathological DD**

| | KS | Pseudo-KS |
|---|---|---|
| Vascular proliferations | Lie back-to-back كتيره و لازقه فى بعض | Separated from each other by edematous stroam |
| Vascular hyperplasia | Independent (**NEW** vessel formation) | Hyperplasia of **pre-existing** BVs |
| CD34 staining | Endothelial lining + spindle cells | Endothelial lining ONLY |

# Cysts of the epidermis (skin)

## *Introduction*

**Cyst = cavity**

1. **Lined with epithelium** (cells touching each other, minimal or no intercellular spaces, resting on BM)
2. **Containing** fluid / semi-solid / solid substance (secretion of wall epithelium)

**Cysts of the skin = cysts of epithelial structures in the skin:**

**A. Epidermis (itself):**

Milium (pl. milia)

**B. Epidermal appendages (adnexa):**

***(1) Hair follicle:***

- **Infundibulum** (like epidermis)
  - Small: Milium (pl. milia)
  - Large: epidermoid cyst (sebaceous cyst اسم خاطئ)
    2 variants:
    a. Pigmented
    b. Vellus
- **Isthmus** (lacks granular layer = abrupt keratinization = compact keratin)
  Pilar (trichilemmal) cyst

***(2) Sweat glands:***

- Eccrine hydrocystoma
- Apocrine hydrocystoma

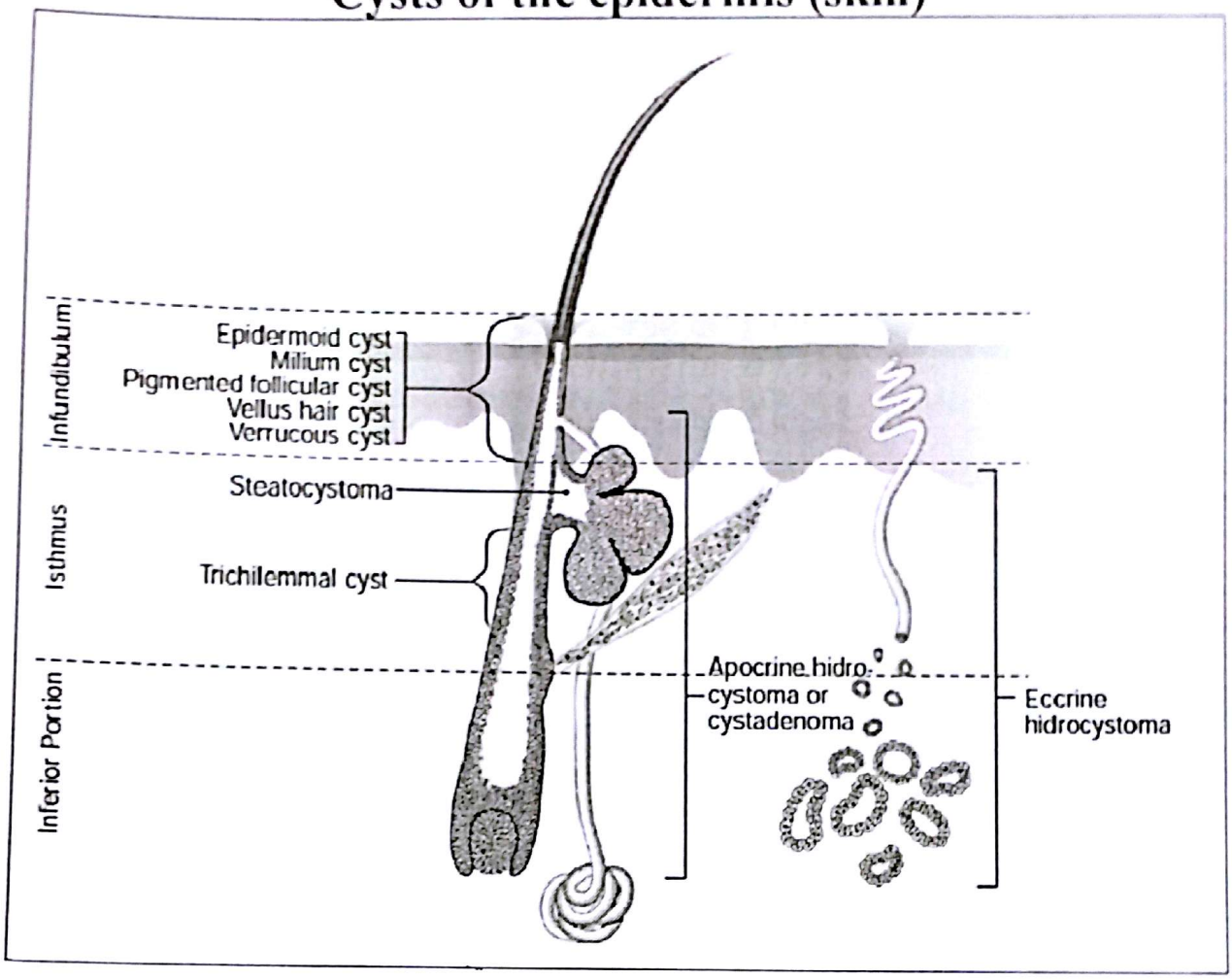
***(3) Sebaceous glands:***

- Steatocystoma multiplex

NB: Histopathology of any cyst (describe wall + contents)

- Wall: origin of cyst
- Contents: secretions of the wall

# Cysts of the epidermis (skin)




## Milium (epidermal, epidermoid cyst)

- Common
- all ages from infancy onwards

**Clinical features:** firm, **white or yellowish**, rarely more than **1 or 2 mm** in diameter - on the **face** (areas of vellus hair follicles, on the cheeks and **eyelids** particularly)

**Types (Aetiology):**
***Primary*** phenomenon
***Secondary*** phenomena following blistering processes (second-degree burns, epidermolysis bullosa, porphyria cutanea tarda and bullous lichen planus), sunbathing, superficial ulceration from trauma or cosmetic procedures, chronic topical corticosteroid-induced atrophy, Dermabrasion, radiotherapy

**Milia in association with syndromes** e.g. hereditary trichodysplasia (Marie–Unna hypotrichosis), oral–facial–digital syndrome type 1 OR BCC-associated syndromes (Rombo syndrome and Bazex syndrome)

*Special variants:*

- **Milia in newborns:** on the hard palate (**Bohn's** nodules) / gum margins (**Epstein's** pearls) – resolve **spontaneously**.
- **Milia en plaque:** multiple milia within an erythematous edematous plaque. Most often occurs in the postauricular area
- **Eruptive:** in young women

**Pathology:**

- Small, thin-walled cysts in the papillary to upper reticular dermis.
- The cysts are lined by a thin layer of stratified squamous epithelium that keratinizes through a granular layer
- Orthokeratin within the cyst cavities is loose and laminated

**Treatment:**

Incision of the epidermis over the milium with a cutting edge needle or sharp-pointed scalpel and squeezing out the contents is usually effective. Recurrence is uncommon. Spontaneous disappearance occurs in many milia in infants.

## Epidermoid cyst

**Synonyms:**

- ☆ Infundibular cyst
- ☆ Epidermal cyst
- ☆ Epidermal inclusion cyst

- the most common cutaneous cysts
- derive from the follicular **infundibulum** (hence the synonym infundibular cysts)

**Clinical features:**

- well-demarcated dermal nodules, and may have a central punctum representing the follicle from which the cyst is derived
- can occur anywhere on the skin, but they are most common on the face and upper trunk
- range from a few millimeters to several centimeters in diameter

They may be **primary**, or they may arise from disrupted follicular structures **or traumatically implanted epithelium** (hence the synonym epidermal 'inclusion' cyst)

**Pathology:**
a cystic cavity filled with laminated keratin lined by a stratified squamous epithelium including a granular layer

**Treatment:**
excision (simple excision, or incision and expression of the cyst contents and wall through the surgical defect)
If the entire cyst wall is not removed, the cyst may recur

**2 variants of epidermoid cyst:**
- Eruptive vellus hair cyst
- Pigmented Follicular Cyst

## Eruptive vellus hair cyst

**Clinical features:**
- **numerous tiny** dome-shaped papules, ranging from skin-colored to darkly pigmented
- most commonly located on the **trunk**
- may be inherited in an **autosomal dominant** pattern

**Pathology:**
a small cystic structure lined by stratified squamous epithelium with epidermoid keratinization. The cysts contain loose laminated keratin and **numerous vellus hairs**

## Pigmented Follicular Cyst

**Clinically:**
This is an uncommon pigmented lesion resembling a nevus
Brown cystic lesion, face and neck, may resemble other pigmented neoplasms, usually solitary

**Pathology:**
Epithelial lining similar to normal epidermis of the **infundibulum** of a hair follicle. Amorphous pigmented keratin in cavity, numerous large pigmented hair shafts. One or two growing hair follicles are seen in the wall of the cyst

**Treatment:**
Vellus hair cysts may be treated by a number of modalities, including incision and drainage, needle evacuation, topical retinoic or lactic acid, and laser ablation.

## Trichilemmal cyst = Pilar cyst

common
Women are affected more frequently than men
middle age

**Clinical features:**
The lesion occurs mainly on the **scalp**
A smooth, mobile, firm and rounded nodule

**Pathology:**
Trichilemmal cysts are lined by stratified squamous epithelium that **lacks granular layer**
The orthokeratin that is produced is eosinophilic and **densely packed**

**Treatment:** excision with a margin (to avoid recurrence).

## Steatocystoma multiplex

Multiple cysts in the dermis having sebaceous gland lobules in their wall and containing sebum.

- Uncommon
- begins in adolescence or early adult life
- both sexes are affected equally

**Clinical features:**

- Multiple, smooth, compressible nodules are present within the dermis, varying in diameter from a few millimeters to 20 mm or more
- usually first appear or become larger at puberty
- The trunk and proximal part of the limbs are most commonly involved, particularly the **presternal area**
- No punctum is usually seen over the cyst, but there may be widespread comedones

**Pathology:**

- The cyst is situated in the mid-dermis.
- The wall is thin and composed of keratinizing epithelium.
- In some sections, lobules of sebaceous glands can be seen to form part of the wall
- The contents are oily, and are composed of the unsplit esters of sebum

**Treatment:**

The number of cysts makes excision impractical in most cases. There is no reason, apart from cosmetic, for treating them.

## Eccrine hidrocystoma

Rare

middle-aged **women**

more common in those who had to work exposed to **heat**, such as cooks.

**Clinical features:**

- The lesions multiple & are confined to the cheeks and eyelids (may be **solitary** and situated close to the **eyelid** ⇨ apocrine hidrocystoma??)
- They are **cystic**, **translucent** or **blue** in colour, a history of **enlargement** when the skin is **exposed to heat** and flattening of the lesion when the skin is exposed to cold.
- Administration of atropine also induces disappearance of the cyst

**Pathology:**

- a dermal cystic lesion uni- or multilocular
- lined by **two layers** of cells
- the **inner** layer of cells is **columnar**
- the **outer** layer consists of elongated **myoepithelial** cells

**Treatment:**

- Electrodesiccation, carbon dioxide laser and pulse dye laser
- Excision
- topical atropine or scopolamine

## Apocrine hidrocystoma

cystic dilatation of apocrine secretory glands

It occurs in adult life

Males and females are equally affected

**Clinical features:**

- **solitary** (or occasionally multiple), well-defined, dome-shaped, translucent nodules
- surface is smooth
- colour varies from a skin colour to greyish or blue-black
- The commonest site is **around the eye, particularly lateral to the outer canthus**
- There are no symptoms
- The cyst increases slowly in size, and may become 10 mm or more in diameter

**Pathology:**

- Large cystic cavities in the dermis
- lined by **cuboidal** or **high-columnar** apocrine secretory cells with **decapitation secretion** and a peripheral layer of myoepithelial cells

**Treatment:**

- ☆ **surgical** removal
- ☆ Other treatment modalities are the same as those used for eccrine hidrocystomas
- ☆ Multiple lesions have been treated successfully with **trichloroacetic acid**

## Dermoid Cyst

- ☆ **subcutaneous** cysts
- ☆ usually are present **at birth**
- ☆ occur most commonly on the **head**, mainly **around the eyes** (external angular dermoid cyst)
- ☆ Dermoid cysts are a result of the sequestration of skin along lines of embryonic closure

**Histopathology:**

Dermoid cysts are lined by an **epidermis** that possesses various epidermal appendages that are usually fully matured

# Epidermal tumors
## Introduction

### Classification:

- **Benign:**
  **(1)** Seborrhoeic keratosis
  **(2)** Keratoacanthoma
  **(3)** Epidermal nevus
  **(4)** Epidermal cysts
  **(5)** OTHERS (warty dyskeratoma, clear cell acanthoma)

- **Malignant:**

  ***Carcinoma in situ (pre-cancerous اسم خاطئ)***
  - Actinic keratosis
  - Bowen's disease
  - Erythroplasia of Queyrat
  - Oral florid papillomatosis
  - Pre-cancerous leukoplakia

  ***Cancerous:***
  - NMSC (SCC, BCC)
  - Paget's disease

**Epidermal cells:**
**(1)** Keratinocytes مهم
- Basal cells
- Squamous cells

**(2)** Dendritic cells

# Seborrhoeic keratosis (SK)

**Definition:** benign epidermal tumor
**Incidence:** **common**
**Epidemiology:**

- Age: **elderly** ($4^{th}$ – $5^{th}$ decade)
- Sex: equal
- Race: more in **fair-skinned** (Caucasians)

**Clinical types:**

**(1) Classic SK:**

- **Asymptomatic**
- Multiple (some times single) sharply defined light brown to black macules and patches ⇨ slightly raised plaque **(stuck-on-surface appearance مهم)**
- Surface: soft velvety or finely verrucous
- Sites: **Face and trunk** (mainly) – Extremities (may be)
  - With the **exception of palms and soles (مهم جدا)**

**(2) Dermatosis papulosa nigra: DPN**

- Affects adult **black** people
- Multiple small pigmented papules
- Affects mainly **malar area of face** and neck, upper trunk

**(3) Stucco keratosis:** ***Non-pigmented variant of SK***

- Non-pigmented (**grayish white**) keratotic papules
- **Bilateral** and **symmetrical** .
- **Distal extremities** (ankles and feet)

**(4) Sign of Leser-Trelat: مهم**

- **Sudden** appearance of **multiple** SKs / **Rapid** increase in number and size
- Associated with **pruritus**
- Affects any body surface
- It's a **para-neoplastic syndrome** (sign of internal malignancy e.g. adenocarcinoma, leukemia…..)
- Course and prognosis: parallels that of the underlying tumor (most of them= aggressive = life span 10.6 months)

*Q How to differentiate:*

- Multiple SKs: gradual onset, long duration, NO pruritus
- Sign of Leser-Trelat: sudden onset, short duration, pruritus

*Q Eruptive (within 6 months) para-neoplastic syndromes:*

1. Sign of Leser-Trelat
2. Acanthosis nigricans
3. Acquired ichthyosis
4. Hypertrichosis languinosa acquisita

**(5) Irritated (inflammed) SK:**

Irritation (e.g. trauma) of any type = crustation and inflammatory base

**Histopathology: ALL types**

- Marked hyperkeratosis, acanthosis and papillomatosis
- **Irregular (church spires)*****
- **Exophytic**: the whole lesion lies above a line from normal epidermis on both sides (clinically: **stuck-on-surface**)
- Proliferation of **2 types of KCs** in the epidermis (**basaloid & squamous**)
- Excessive keratinization ⇨ **horn cyst** and **horn pseudo-cyst** (invagination of stratum corneum)

***Histopathological variants:*** *أسماء فقط*

1. Acanthotic (Classical)
2. Hyperkeratotic (Papillomatous)
3. Reticular (Adenoid)
4. Irritated
5. Melanoacanthoma
6. Clonal (Nesting) type "Borst–Jadassohn phenomenon"

**Treatment**: removal for cosmetic purpose

- Surgical removal (shave excision)
- Sharp curettage
- TCA
- Cryotherapy
- Electrocautery
- Lasers (CO2, Er:YAG)

# Keratoacanthoma (KA) البركان

**Definition**: **rapidly-growing self-healing** benign epidermal tumor
***Clinically and histopathologically resembling SCC*** مهم جدا

**Clinical types:**

1. Solitary KA
2. Multiple KA

## Solitary KA

**Epidemiology:**

- Age: elderly > 45 yrs
- Sex: more in males (3:1)
- Race: fair-skinned

**Clinically:**

- Firm skin-colored to pink dome shaped papule / nodule with **keratin filled crater in its center** مهم
- Evolves rapidly (**proliferative** phase), reaches its full size in short duration (1-2 cm within 6-8 weeks) "**mature** phase"
- Involutes spontaneously in < 6 months with slightly-depressed scar "**involution** phase"

زى البركان (تطلع بسرعه و تكبر بسرعه و تنزل بسرعه = تخف لوحدها)

**Sites: NOT IN PALMS & SOLES**

- Mostly: **sun-exposed areas** e.g. face
- Also: hairy areas, subungual (painful & tender)

**DD: SCC**

KA (younger age of onset, more rapid evolution, on normal skin, spontaneous healing)

**Histopathology**:

- Better seen on **low power magnification "scanning view"**
- Large central keratin-filled crater
- Epidermis on either side of the crater extends like **shoulders**
- Irregular **epidermal proliferations at the base** of the crater BOTH upwards in the crater and downwards into the dermis ***(resembles SCC BUT in KA = more keratinization)***
- Dermis: lympocytic infiltrate

**Treatment:**

**NO treatment (self-limited)**

- Surgical excision and biopsy (better cosmetic results & to exclude SCC)
- Curettage
- Cryotherapy
- Electrocautery
- 5-FU

## Multiple KA

2 main variants

| Multiple familial self-healing epitheliomas **(Ferguson-Smith)** | Generalized eruptive KA **(Grzybowzki)** |
|---|---|
| Early onset (adolescents) | Late onset (adults) |
| More in males | Equal sex |
| Family history | NO Family history |
| May be inherited (AD) | NO inheritance |
| Few (3-10) lesions | Hundreds of small (2-3 mm) lesions |

**Histopathology**: similar to solitary KA

**Treatment**: acitertin and MTX

## Epidermal (Verrucous) nevus

**Definition**: hamartomatous lesions of epidermis and papillary dermis

**Epidemiology**:

- Incidence: 1/1000 infants
- Age of presentation: 80% within 1st year of life
- Sex: equal
- Sporadic (mainly) – may be familial

**Cells of origin:** pluripotent stem cells in the basal layer of the epidermis

**Clinical features: 2 main types**

***(1) Localized type (Nevus unis lateris):***

- Closely-set skin-colored / brown papules with verrucous surface
- Unilateral (only on one side)
- Any site, mostly extremities (longitudinal) or trunk (transverse or curved)

*(2) Systematized type (ichthyosis hystrix)*

- Bilateral and symmetrical
- Widespread
- Linear

**Histopathology:**

- Marked compact hyperkeratosis, acanthosis, papillomatosis and elongation of rete ridges (كل حاجه تزيد فى مكانها)
- In systematized type, epidermolytic hyperkeratosis may be seen

**Associations (especially systematized type):**
Congenital anomalies (CNS ⇨ epilepsy, skeletal …)
DO MRI and other imaging studies

**Malignant transformation:**
BCC and SCC (less common): RARE

**Treatment:**

- If systematized, evaluate for systemic affection
- Removal for cosmetic purpose:
  - Full-thickness surgical excision and grafting
  - Shave excision and curettage (recurrnce)
  - Läser ablation

# Actinic / senile / solar keratosis

***The most common pre-malignant (carcinoma in situ) skin lesion***

**Epidemiology:**

- Age: **elderly**
- Sex: more common in **males**
- Skin phototype: **fair** complexion (with excessive sun exposure, sunburn easily and tan poorly)

**Risk factors:**

- Fair skin
- Excessive UV exposure including Sun ray reflection (snow)
- High altitude
- Ionizing radiation
- Genodermatoses e.g. albinism and XDP

**Clinical features:**

***Classic (Erythematous) types:***

- Sites: **sun-exposed areas** (bald scalp in men, face, dorsa of hands)
- Lesions: multiple **ill-defined** erythematous macules and patches ⇨ papules up to 1 cm in diameter, usually covered by **scales**, with **NO or little infiltration**

***Clinical variants / Types of AKs (clinic-pathological):***

- Pigmented type (pigmented with peripheral spreading)
- Cutaneous horn-like (excessive hyperkeratosis)
- Actinic cheilitis (AK on the vermilion border of the lower lip with scaling and erosions)
- Other: Atrophic, Hypertrophic, Proliferative, Acantholytic, Bowenoid, Solitary lichenoid

**Course:**

- Some lesions **may disappear simultaneously**
- 20% of cases **may progress to SCC** after **long period of latency (up to 10 years)**
- ***Features suggestive of progression:*** increased (erythema, size "diameter", thickness), ulceration, pain and hemorrhage

**Histopathology:**

***Epidermis:***

- **Atypical** KCs (pleomorphism, loss of polarity and arrangement)
- Limited to the **lower part of the epidermis** مهم جدا
- **Spares adnexal structures** مهم جدا
- Alternating
  - **Ortho**-hyperkeratosis (over acro-syringea and acro-trichia)
  - **Para**-keratosis (over atypical KCs)
    **= pink and blue sign (Flag sign)** مهم جدا

***Basement membrane area:*** intact, NO invasion into dermis

***Upper dermis:*** signs of solar elastosis + chronic inflammatory infiltrate

**Treatment:**

- Sun avoidance / protection (sunscreen)
- Surgical excision
- Curettage
- Cryotherapy
- Electrocautery
- 5-FU
- Imiquimod
- Topical retinoids
- PDT
- TCA

***Radiotherapy is contraindicated*** مهم جدا

# Bowen's disease

**Risk factors:**

- Chronic sun exposure
- Arsenic ingestion / toxicity
- Epidermodysplasia verruciformis (HPV5)
- Porokeratosis

***In the majority of cases, NO risk factor can be identified***

**Clinical features:**

***Sites:***

- Sun-exposed areas: chronic sun exposure
- Sun-covered areas: arsenic

***Lesions:***

- **Single** (usually)
- **sharp** but **irregular** erythematous slowly-enlarging patch
- With areas of **scaling** and crustation
- With little or no infiltration

**Course:** Progression to SCC (5-11 % of cases)

**DD:** مهم جدا

- Bowen's disease
- Superficial BCC (pearly beaded border)
- Paget's disease
- Eczema
- Dermatophyte infection (T. corporis)
- Psoriasis
- Patch stage of MF

**Histopathology:** ***intra-epidermal SCC / SCC in situ***

***Epidermis:***

- Hyperkeratosis, **parakeratosis**, acanthosis, **broadening** علامه مهمه of rete ridges (why?)
- Atypical KCs (???) affecting the whole thickness مهم جدا of the epidermis and adnexal structures with complete loss of arrangement of KCs (wind-blown appearance)
- Dyskeratotic cells

***Basement membrane area:*** intact, NO invasion into dermis

**Histopathological DD مهم جدا**

| AK | Bowen's |
|---|---|
| Lower epidermis | Whole thickness |
| NO adnexal affection | Affected adnexa |
| Alternating ortho- and para-keratosis | Para-keratosis |

**Treatment:**

- Sun avoidance / protection (sunscreen)
- Surgical excision
- Curettage
- Cryotherapy
- Electrocautery
- 5-FU
- Imiquimod
- Topical retinoids
- PDT
- TCA

***Radiotherapy is contraindicated مهم جدا***

## Erythroplasia of Queyrat
## = Bowen's disease of the glans penis

- Almost exclusively **old uncircumcised men**
- Single / multiple sharply-demaracted bright red patches and thin plaques on glans penis and coronal sulcus
- Histopathology, course and TR: **like Bowen's**
- **BUT more risk for progression to SCC (30%)** and the developed SCC is **more aggressive** with **more tendency to metastasize**

## Oral florid papillomatosis

- White **cauliflower**-like lesions involving large area of oral mucosa
- May extend to larynx and trachea
- **Rare metastasis**, limited to regional LNs
- Progression to verrucous carcinoma OR a form of verrucous carcinoma with low metastasis (DEBATE)

# Leukoplakia

- **Common** disorder
- A **descriptive** term = ***white patch or plaque affecting mucosa*** (adherent and can't be rubbed off) i.e. **non-specific** term
- May be
  - **Benign**: chronic irritation (smoking, ill-fitted dentures), candida, LP …etc
  - Carcinoma in situ / carcinoma: SCC
- Managed according to type and underlying pathology

# Paget's disease

(1) Of the breast (nipple)
(2) Extra-mammary

## Paget's disease of the breast (nipple)

**Age**: **old** 55 yrs
**Sex**: almost exclusively in **women** (case reports in men)

**Clinical features:**

- **Unilateral** مهم جدا
- Areola and nipple
- Sharply-defined slightly-infiltrated erythematous patch with oozing, crustaion, scaling, ulceration and may be nipple retraction

**Associations:**
Intra-ductal **carcinoma of the breast** مهم جدا
(may be palpable mass in the breast or axillary LN ++)

**Histopathology:**
***Epidermis: large numbers of Paget's cells***

- At different levels of the epidermis
- Singly or in groups
- **Large** cells with round nuclei and ample pale cytoplasm (containing glycogen مهم جدا)
- ***NOT in basal layers i.e. supra-basal***

***Upper dermis:*** chronic inflammatory infiltrate

**DD:** مهم جدا

- **Eczema (bilateral usually)** مهم جدا
- Bowen's disease
- Superficial BCC (pearly beaded border)
- Paget's disease
- Dermatophyte infection (T. corporis)
- Psoriasis
- Patch stage of MF

**Histopathological DD:** ***pagetoid patterns*** **********

(1) Paget's disease
(2) Pagetoid MM in situ (basal layer, invade dermis, S100, HMB45)
(3) Pagetoid reticulosis (MF)

**Origin of Paget's cells:**
Glandular origin (apocrine, eccrine)
+VE stain with carcino-embryonic antigen (CEA)

**Treatment:** modified radical mastectomy (MRM)

## Extra-mammary Paget's disease

**Sites**: areas with **apocrine** glands

- Vulva, urethra
- Scrotum, glans penis, urethra
- Peri-anal region

**Clinical**: as mammary type but **itchy**

**Underlying cancer** (cervix, urinary baldder, rectum)

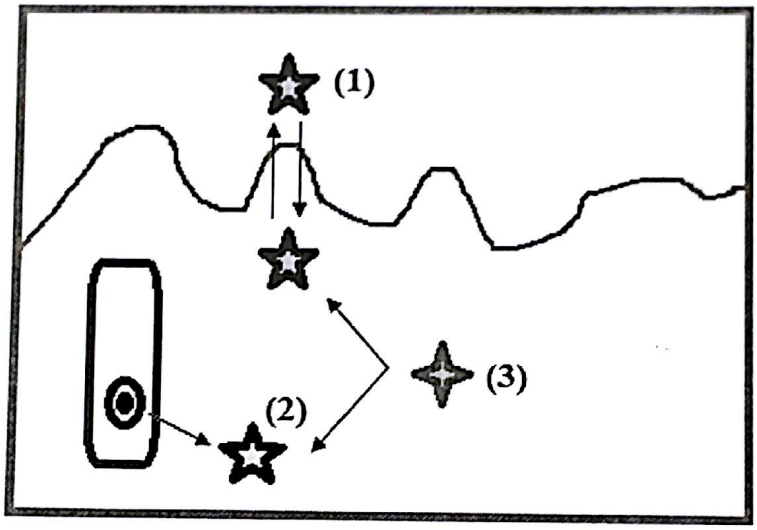
**Treatment**: of the underlying malignancy

# Histiocytoses

## Introduction

- **Histiocytoses:** a group of proliferative disorders characterized by proliferation of **histiocytes (tissue macrophages)** مهم in the **skin** and/or **other tissues**

- **Three 'histiocytes' of cutaneous importance:**
  1. **Langerhans cell (LC):** in the **epidermis** – migrates to and from the epidermis – **APC**
  2. **Mononuclear cell/macrophage (the 'true' histiocyte):** in the **dermis** – migrates to and from the dermis – both **phagocytic** and **APC** (derived from **blood monocyte**)
  3. **Dermal dendrocyte:** in the **dermis** – a reservoir of pluripotential mononuclear cells ⇨ both phagocytic and APC




**Classification of Histiocytoses:**

1. **Langerhans cell histiocytosis (LCH)**
2. **Non-Langerhans cell histiocytosis (non-LCH)**

| | LC Histiocyte | NLC Histiocyte |
|---|---|---|
| **H&E** | **large**, 10-15μm in diameter with **pale sytoplasm** and **reniform (kidney-shaped) nucleus** | |
| **Immuno-histochemistry** | **CD1a** (most specific)<br>Others: S100, ATPase, peanut lectin , α-D-mannosidase, Langerin (CD207) | **CD68** (most specific)<br>Others: Mac387 or HAM56 |
| **E/M** | **Birbeck granules:** rod- or racquet-shaped cytoplasmic structures (pathognomonic) | **Comma-shaped bodies** |

# PART 1: Langerhans cell histiocytosis (LCH)

Previously "**Histiocytosis X**" = unknown زمان – إسم قديم

**Types:** A disease **spectrum** with **four** main types:

(1) Letterer–Siwe disease = Acute disseminated / diffuse form
(2) Hand–Schüller–Christian disease = chronic multi-focal form
(3) Eosinophilic granuloma of bone = benign localized form
(4) Hashimoto–Pritzker disease = Congenital self-healing reticulohistiocytosis

## Clinical picture:

***General:***

Ranges from **mild asymptomatic single-organ** involvement to **severe progressive multisystem** disease

| **Letterer–Siwe disease = Acute disseminated / diffuse form** | **Hand–Schüller–Christian disease = chronic multi-focal form** | **Eosinophilic granuloma of bone = benign localized form** | **Hashimoto-Pritzker disease = Congenital self-healing reticulohistiocytosis** |
|---|---|---|---|
| **Age** < 2 years | 2 – 6 years | Older children | At/few days after birth |
| **Skin:** 1-2 mm pink to skin-colored **papules, pustules and/or vesicles** *scalp, flexural areas (neck, axilla, perineum, trunk) *2$^{ry}$ changes: scale, crust, secondary impetiginization | **30% of cases** *Early: like Letterer–Siwe *Late: xanthoma-like **MM lesions:** **Oral/genital** Ulcerative nodules on gingiva = premature loss of teeth | **RARE** Skin & MM lesiosn | **Limited to the skin** Red to brown papulo-nodules. After **several weeks, lesions crust and involute** **MM lesions are rare** |
| **Systemic: Multi-systemic disease** – many organs may be affected (liver, spleen, lung… | **Triad** **Diabetes insipidus** *Infiltration of post. Pituitary = ↓ ADH* **Bone lesions** **Exophthalmos** | **Single** asymptomatic granulomatous lesion of **bone** **Spontaneous fracture** may be the first sign Most common site: skull – others (long bones, ribs) | **Rare** |
| **Prognosis: poor** | Chronic progressive course | | Rapidly self-healing |

*Malignancy association:* Increased incidence of **solid tumors** and **leukemia**

## Aetio-Pathogenesis

**Unknown**

- **Genetic:**
  - Some cases are hereditary
  - Clonal CD1a+ histiocytes in all LCH tissue
- **Environmental triggers: Viral** = human herpesvirus type 6 (HHV-6) ??? (controversy)
- **Immunologic disturbance:** elevated levels of cytokines in lesions of LCH e.g. TNF-α, IFN-γ, GM-CSF, IL-1, IL-2, IL-4 and IL-10, …

## Prognosis

- **Varies** dramatically.
- A **high mortality rate** is associated with:
  1. multi-system disease
  2. children less than 2 years of age
  3. any patient with multi-organ disease (if the hematopoietic system, liver, lungs or spleen is involved)

## Histopathology

Proliferation of **LCH cells** is present in the **papillary dermis** (توصف كما سبق)
***The cytoplasm of the reticulohistiocytes = 'ground glass' appearance*** خاص
**Immuno-histochemical staining:** كما سبق
**Electron microscopy:** كما سبق

## Differential diagnosis of cutaneous lesiosns:

- ***Letterer–Siwe disease:*** Seborrheic dermatitis, scabies, eczema, varicella, intertrigo, Darier disease, candidiasis, urticaria pigmentosa, mycosis fungoides
- ***Bony lesions:*** leukemia, lymphoma, multiple myeloma
- ***Non-Langerhans cell histiocytoses*** ازاى؟؟

## Treatment

1. **Evaluation** of hematologic, pulmonary, hepatic, renal and skeletal ….. systems (to determine the extent of disease).
2. **Choice** of treatment **depends on** the **number** of body systems involved and **severity** of involvement.

**Mild single-system skin disease:**

- topical corticosteroids
- topical antibacterial agents
- PUVA
- topical nitrogen mustard (mechlorethamine)

**More extensive disease:** thalidomide

**Bone lesions:**

- *Localized:* curettage.
- *Symptomatic recurrent or new lesions, or those with a significant risk of fracture, cosmetic defect or functional abnormality:* radiation.
- *Less problematic bone tumors:*
  - oral NSAIDs
  - Intralesional corticosteroid injections.

# PART 2: Non-Langerhans cell histiocytosis (non-LCH)

**Classification – simplified (6)**

- ***Primarily cutaneous, usually self-resolving:***
  **(1) Juvenile xanthogranuloma (JXG)**
  **(2) Benign cephalic histiocytosis**
  **(3) Generalized eruptive histiocytoma**
- ***Primarily cutaneous, often persistent/progressive:***
  Papular xanthoma
  Progressive nodular histiocytoma
- ***Frequent systemic involvement:***
  **(1) Necrobiotic xanthogranuloma (NBX)**
  **(2) Multicentric reticulohistiocytosis (MCR)**
  **(3) Xanthoma disseminatum**
- ***Systemic with rare skin involvement:***
  Erdheim–Chester disease
  Hemophagocytic lymphohistiocytosis (HLH; hemophagocytic syndrome)
  - Primary (genetic)
  - Secondary (acquired)

الفكرة العامة
***Site of involvement:*** **cutaneous / systemic**
***Course:*** **self-healing / progressive**

# Juvenile xanthogranuloma (JXG)

## Epidemiology

- **Incidence:** a fairly **common** disorder
- **Age and Sex:**
  - In childhood: **male** predominance
  - In adults: **no sex predilection**
  - Almost 75% of cases during the **first year** of life (***the most common histiocytic disease of childhood***) مهم جدا جدا

## Clinical picture:

***Skin:***

Pink to red–brown, dome-shaped papules and nodule, 2–5 mm in diameter
Rapidly become **yellow**
The most common location: **head and neck**

***Extra-cutaneous lesions:***

(1) The **eye** (**most commonly** affected): **Ocular JXG = Hyphema** (hemorrhage into the anterior chamber) and **glaucoma** - can result in **blindness**. Early referral to an ophthalmologist for evaluation and possible treatment is important.
(2) The **lung** is the **second** most frequent extracutaneous site of disease
(3) Others: Visceral, bone and CNS involvement is rare

***Association with:***

café-au-lait macules / NF1 / juvenile myelomonocytic leukemia
**Triple association: مهم JXG, NF1, juvenile myelomonocytic leukemia**

## Prognosis:

- limited to the skin, self-limited and benign
- patients are otherwise in good health
- lesions usually regress within 3-6 years

## Histopathology:

*Dense infiltrate of **histiocytes** in the superficial dermis (توصف)
* Mature lesions: histiocytes develop **lipid** in their cytoplasm, creating a foamy **'xanthomatous'** appearance. **Touton giant cells** are a characteristic finding مهم
* **Immunohistochemistry: CD68**, HAM56, factor XIIIa, S100 **(-ve CD1a)**
* **Electron microscopy: comma**-shaped bodies, lipid vacuoles, cholesterol clefts, and myeloid bodies in the histiocytes.

**DD** (histopathologic examination)

- **Xanthoma**
- Spitz nevus
- Pyogenic granuloma
- Keloid
- Molluscum contagiosum

***Other NLCH***

- Benign cephalic histiocytosis
- Generalized eruptive histiocytoma
- Xanthoma disseminatum

## Treatment:

**Cutaneous lesions:** self-limiting (no treatment is required). Lesions may be removed for cosmetic concerns

**Ocular lesions:**

- topical corticosteroids for iris lesions
- excision for limbal lesions

**Systemic involvement:**

Followed without treatment unless their location interferes with normal function:

- chemotherapeutic regimens
- Radiotherapy
- high-dose corticosteroids
- cyclosporine

## Benign cephalic histiocytosis

**Very Rare**

**Age:** within the first 3 years of life

**Sex:** no gender predilection

**Clincal features:**

- 2-5-mm, red to red–brown **macules and papules**
- first on the **face** ⇨ subsequent appearance on the ears and neck
- Occasionally, lesions may develop on the trunk and arms

**Pathology:** As NLCH (page 69) عادى جدا

***Touton cells are absent and foamy cells are rare or absent (NO lipid accumulation).*** مهم جدا للتفرقه

**Differential diagnosis: LCH and other non-LCH disorders:** JXG, Generalized eruptive histiocytoma

**Prognosis:**

- **Spontaneously resolve** after months or years
- Lesions flatten, become hyperpigmented, and disappear completely
- Most children are otherwise healthy without involvement of the mucous membranes or internal organs

**Treatment:**
NO treatment is required (self-limited)

## Generalized eruptive histiocytoma

**Epidemiology**

- **Very rare** disease
- **Age:** children (< 4 years) adults ($3^{rd}$ – $6^{th}$ decade)
- **Sex:** There may be a **male** predilection

**Clinical features:**

- recurrent crops of hundreds of red to brown papules, less than 1 cm
- on the face, trunk and proximal extremities
- In **adults**, symmetric & mucosal surfaces are involved
- In **children**, asymmetric & mucous membranes are not involved

**Prognosis:**

- Within several months, the lesions **resolve completely** or leave behind hyperpigmented macules or small scars
- the affected individuals are **otherwise healthy**.
- **Internal involvement** has **not** been observed

**Pathology:** As NLCH (page 69) عادى جدا

**DD:**

- LCH, and other non-LCH disorders e.g. Xanthoma disseminatum:
- urticaria pigmentosa
- eruptive syringoma
- eruptive xanthoma
- PLEVA/PLC
- Miliary (popular) sarcoidosis

**Treatment: No treatment** is required (self-limited, NO systemic symptoms) + Careful follow-up of all patients

## Reticulohistiocytoses

- **Rare group** of closely related NLCH, Most commonly affect **adults**
- A **spectrum** of disease
  - a **solitary cutaneous** form: **giant cell reticulohistiocytoma = Solitary reticulohistiocytosis = Solitary reticulohistiocytoma**
  - **multicentric reticulohistiocytosis** (a disease with both cutaneous and systemic features)

BOTH forms = classic histopathology: mononucleated & multinucleated giant cells with a **'ground glass' appearance** مهم جدا
*Histiocytes have abundant eosinophilic, homogenous, and finely **granular cytoplasm**, creating a **'ground glass' effect**

## Multicentric reticulohistiocytosis

**uncommon**, occurring most frequently in **women** during the **fourth decade**.

**Cutaneous lesions:**

- skin-colored to red, brown or yellow papules and nodules
- **acrally** distributed (head, hands, fingers, ears, articular regions of limbs)
- Small papules along the periungual regions **'coral bead' appearance** مهم
- '**leonine facies**' secondary to severe facial involvement
- Affection of the oral, pharyngeal and nasal **mucosa** (50% of cases)

**Extra-cutaneous lesions:**

- **Arthritis: symmetric**, **erosive** (progression to arthritis mutilans) / joints of the fingers and hands, knees and wrists
- **Cartilaginous destruction** of the nose and ears can lead to **facial disfigurement**
- **Rarely: histiocytic involvement** of the heart, eye, lungs, thyroid, liver, kidney, muscle, salivary gland and/or bone marrow

**Associations:**

- Fever and weight loss
- Hyperlipidemia & Hypercholesterolemia
- positive tuberculin skin test
- systemic vasculitis
- autoimmune disease
- malignancy (up to 28% of patients): bronchial, breast, stomach and cervical carcinomas being most common
- elevated ESR and anemia
- IgG hypergammaglobulinemia & Cryoglobulinemia

**Patholgy:** As NLCH + **'ground glass'** appearance

**DD:**

- **Solitary reticulohistiocytoma:** Other conditions with a **single nodule** e.g. solitary adult xanthogranuloma, Spitz nevus, adnexal tumor, Dermatofibroma, atypical fibroxanthoma
- **Multicentric reticulohistiocytosis:** other NLCH + **rheumatoid arthritis** (arthritis plus nodules overlying joints) + **papular mucinosis**

**Treatment:**

- **Solitary reticulohistiocytoma:** Surgical excision is curative
- **Multicentric reticulohistiocytosis:** methotrexate, either alone or in combination with cyclophosphamide and corticosteroids

## Xanthoma disseminatum

- Rare, Any age, More in males

**Clinical features:** <u>triad</u> of

1. **Cutaneous xanthomas**
   yellow, red or brown papule
   **hundreds** of papules, symmetrically arranged, on the face, flexural and intertriginous areas of the trunk and proximal extremities
   lesions tend to **cluster** into well-formed **disfiguring** plaques
   older lesions may become åtrophic
2. **Xanthomas of mucous membranes**
   40-60% of patients - Most commonly: upper airway & oral mucosa
3. **Diabetes insipidus:** CNS involvement: hypothalamus & pituitary stalk

**Pathology:** dense dermal infiltrate of **histiocytes** (as NLCH عادى), **foam cells and Touton cells**

**Differential diagnosis:**
***Other causes of histiocytes of Diabetes insipidus (???)***, eruptive xanthoma, generalized eruptive histiocytoma, papular xanthoma, and multicentric reticulohistiocytosis.

**Treatment**
<u>Radiotherapy:</u> to control airway obstructive disease
<u>Cyclophosphamide</u> (effective in the control of mucosal lesions)
<u>Cutaneous lesions:</u> CO2 laser, dermabrasion, radiotherapy, excision, electrocoagulation, intralesional corticosteroids, cryotherapy

# Adnexal tumors

**Adnexa = skin appendages = epidermal appendages:**
ALL derived from epidermis – include:

- Hair follicles
- Sebaceous glands
- Sweat glands (Eccrine /Apocrine)

## (A) Tumors with follicular differentiation

1. Trichofolliculoma
2. Trichoepithelioma
3. Pilomatricoma

### 1. Trichofolliculoma

**Definition:** A benign follicular tumor

**Clinical features:**

- a **papule** or **nodule**
- involving the **face**, scalp or upper trunk
- sometimes, a central follicular **ostium (punctum)** may be present and it may contain a small **tuft of immature hairs (vellus)**

**Pathology:**
A **central** cystic space with **infundibular** cornification and central orthokeratin. Well-developed **vellus follicles** protrude in **radial** fashion from this central structure.

***Enlarged hair follicle filled with keratin with small follicles protruding from the wall (inverted tree appearance)***

**Treatment:**

- **Surgical excision**
- Trichofolliculoma is **wholly benign** and **no treatment** is needed. If a trichofolliculoma is discovered by biopsy, no further intervention is required.

### 2. Trichoepithelioma

**Definition:** Benign follicular neoplasm

**Clinical features:**

- a skin-colored **papule or nodule** on the **face** or upper trunk with predilection for the **nose**

- **2 types:**
  - ***Single (solitary):***
    - More common
    - Non-hereditary
  - ***Multiple (epithelioma adenoids cysticum or Brooke's disease):***
    - **Familial**
    - highest density of lesions in the **central face**
    - associated with a risk of secondary BCC or other tumors

**Pathology:**

Masses (clusters) of follicular germinative **cells** with enveloping **fibrocytic stroma** (simulate BCC مهم جداً)

- fibrous **stroma** is tightly **adherent** to follicular germinative cells (in BCC, clefts between basaloid cells and stroma ⇨ diagnostic clue)
- tumor **cells** show **follicular differentiation** e.g. small cornifying cystic spaces

***Masses of basaloid cells (like BCC) BUT adherent stroma (cleft in BCC) & follicular differnetiation***

**Treatment:**

- **Solitary** trichoblastoma is benign and needs no surgical treatment.
- **Multiple** facial trichoepitheliomas can be **cosmetically disabling** and many affected patients desire some type of intervention
  - Close **follow-up** for the possibility of secondary **BCC**
  - Because of the number of lesions, **conventional excision is not indicated**
  - Other **ablative approaches**, including **laser** or **electrosurgical** destruction, have been employed with some success

## 3. Pilomatricoma

(pilomatrixoma, trichomatrioma, ***calcifying*** epithelioma)

**Definition:** A benign follicular neoplasm

**Clinical features:**

- a **solitary** skin-colored or bluish **nodule** (rarely, multiple)
- **Firm** مهم جداً (due to secondary **calcification** + fibrosis and granulomatous inflammation). Some lesions are **"rock-hard"**
- involve the **head or upper trunk**
- Most common in **childhood** مهم جداً and adolescence (may develop at any age)

**Pathology**

- *Early pilomatricoma:*
  - **cyst** with central matrical cornification
  - cyst wall: basaloid matrical cells ⇨ abrupt transition to central eosinophilic cornified matrical cells (lose their nuclei)
  - The **central anucleate cornified cells** are commonly referred to as **ghost or shadow cells** مهم جداً.
- *Fully-developed lesions:*
  - The cornified matrical cells elicit **fibrosis** and a **secondary granulomatous infiltrate**
- **Calcification** and **ossification** in late lesions

***Masses of basaloid matrical cells. Later, cells lose nuclei (ghost cells). Later, calcification***

**Treatment**

- Pilomatricoma is a **benign** lesion that is usually treated by simple **enucleation** or **complete excision**
- A pilomatricoma may **recur** after **limited excision**

## (B) Tumors with sebaceous differentiation

- **Ectopic sebaceous glands:** Fordyce's Spots / Montgomery's tubercles
- **Hyperplasia (↑ size of Single sebaceous gland):** Sebaceous gland hyperplasia
- **Hamartoma: (↑ size and number of multiple sebaceous glands + <u>other elements</u>):** Nevus Sebaceus of Jadassohn
- **Cysts:** Steatocystoma multiplex
- **Benign tumors:** أسماء فقط
  - Sebaceous adenoma (**mature** sebocytes > basal immature seboblasts)
  - Sebaceoma (basal **immature** > seboblasts mature sebocytes)
- **Malignant tumors:** أسماء فقط Sebaceous carcinoma
- **Syndromes:** Muir-Torre syndrome

### 1. Ectopic sebaceous glands

**Clinical Presentation:**

- *Fordyce's Spots:*
  - **Tiny** white or yellow discrete **papules**
  - Vermilion border of the **lips**, particularly **upper lip**, genital skin, or on the oral mucosa
- *Montgomery's Tubercles:*
  - Tiny slightly raised 1 to 2 mm papules on the **areolae** of breasts. Present in nearly **every adult woman** and sometimes in men

**Histopathology:**

- A single sebaceous gland or lobules in the submucosa or dermis
- **Direct opening onto the surface (مهم جداً)**

## 2. Sebaceous gland hyperplasia

**Definition:**

Benign **enlargement** of sebaceous glands (not a true neoplasm)

**Clinical features:**

- a relatively **common** condition
- **one or multiple yellowish**, occasionally telangiectatic **papules** with a **central depression** (a central follicular infundibular ostium)
- usually on the **central or upper face** and sometimes on the upper trunk

**Pathology:**

- Biopsy is occasionally indicated to exclude BCC.
- The sebaceous gland shows **normal morphology** (a thin rim of **seboblasts** surrounding the remainder of the gland, composed of **mature sebocytes**)
- **Enlarged** sebaceous lobules surround a central infundibulum.

**Treatment:**

- If treatment is desired, lesions can be **removed** or **diminished** by shave, light electrosurgical destruction, cryotherapy, or laser ablation
- Long-term **topical retinoid** application may be beneficial
- **Oral isotretinoin** for patients with extensive disfiguring lesions.

## 2. Nevus sebaceous of Jadassohn (organoid nevus)

**Definition:**

× Nevus sebaceus is commonly thought of as a sebaceous lesion

✓ In truth, nevus sebaceus is a **non-neoplastic nevus** or **congenital malformation** that includes **follicular**, **sebaceous** and **apocrine** elements

**Clinical features:**

- involves the **scalp** or **face** (commonly), neck (occasionally), trunk (rarely)
- **linear** lesions are distributed along the **lines of Blaschko**

1. **At birth**, only **slightly raised**
   - On the scalp, a nevus will remain **hairless**, or mostly so, as the infant's hair grows around it
2. **During childhood**, the nevus **thickens** slightly and assumes a **yellow or orange** hue
3. **At adolescence**, progressive thickening - the surface becomes **verrucous**
4. Nevus sebaceus represents a fertile field for the development of **secondary adnexal neoplasms**, commonly **benign** الأكثر but occasionally malignant
   - The vast **majority** of secondary proliferations represent **benign** follicular (**trichoblastoma**-like) foci
     - ☆ Historically, **syringocystadenoma papilliferum (papillary syringoadenoma)** was believed to represent the **most common** secondary proliferation
     - ☆ recent analysis indicates that **trichoblastoma** holds this role
   - The actual incidence of secondary basal cell carcinoma (**BCC**) is **less than 1%**
   - Only **rarely** does secondary sebaceous **carcinoma** or apocrine carcinoma arise in a nevus sebaceus. Malignancy probably develops only in **longstanding or neglected** lesions but exceptionally can be a source of **mortality**.
   - **Other common secondary neoplasms** include trichilemmoma, desmoplastic trichilemmoma, sebaceous adenoma, apocrine adenoma, and poroma

**Patch of alopecia ⇨ thick yellowish ⇨ verrucous ⇨ 2$^{ry}$ tumors (benign > malignant)**

## Pathology:

1. (قراءة فقط) Infantile nevus: microscopically changes (malformed follicular units are small and deviate little from normal)
2. (قراءة فقط) During later childhood: tiny misshapen lesional follicles (in contrast to normal terminal follicles at the periphery of the biopsy) + small apocrine glands (deep) + epidermis thickening (more papillated like epidermal nevus)
3. **By late adolescence: (well-developed nevus sebaceous)** هو ده المهم
   - ☆ **Epidermis: acanthosis** and fibroplasia of the papillary dermis (identical epidermal nevus)
   - ☆ **Sebaceous glands:** enlarged & increased in number
   - ☆ **Apocrine glands:** dilated & increased in number (in the reticular dermis – deep)
     - This histopathology remains stable into adulthood.
   - ☆ Over time, some patients develop exaggerated **verrucous epidermal hyperplasia** much like a **verruca vulgaris** (may be due to HPV infection)
4. **Secondary neoplasms** are common e.g. trichoblastoma, trichilemmoma..

**Hyperplasia of (3): epidermis + sebaceous + apocrine glands (so, called *organoid nevus)* ⇨ later: 2$^{ry}$ tumors**

**Treatment:**

**(1) Complete excision**

- *Why?*
  - becomes increasingly verrucous and **unsightly** over time
  - × the risk of development of secondary carcinoma is low
  - × the risk for the development of a secondary benign neoplasm, e.g. syringocystadenoma or trichoblastoma, is relatively high
- *When?*
  - **early** (during childhood, before the development of secondary verrucous alteration) ⇨ risk of scarring is reduced compared to adulthood.

**(2) Removal** by **shave** or **laser** ablation is usually **not successful**.

**(3) Conservative approach:** follow up (wait and see)

- × the risk of development of secondary carcinoma is low

*Muir-Torre syndrome*

- **Autosomal dominant**
- **Sebaceous** tumors (often **multiple**) + **visceral** neoplasms
- ***Visceral tumors:***
  - Usually of the **GIT**: polyps of the large bowel & adenocarcinomas
  - Other organs e.g. larynx, the genito-urinary system, ovary, and uterus
- ***Sebaceous tumors*** e.g. Sebaceous adenoma, Sebaceoma, Sebaceous carcinoma, BCC with sebaceous differentiation

## (C) Tumors with apocrine/eccrine differentiation

1. Syringoma

## 1. Syringoma

**Definition:**a benign adnexal neoplasm with **ductal(syringeal)** differentiation of **eccrine**(or apocrine) lineage

**Clinical features**

- a small, firm, skin-colored papule.
- commonly **multiple** and maybe **eruptive**
- affects**women** more commonly than men
- may occur at any site on the body but more in the **periorbital** area, especially the **eyelids**. Sometimes, lesions involvethe upper trunk, favoring the ventral surface, or genital skin
- **Eruptive** syringomas most commonly involve the **trunk**

**Histopathology:**

- A small and **circumscribed** mass confined to the **superficial dermis**
- The **epithelial component**: cells with pale or pinkish cytoplasm forming **nests** and**tubules**(ductular differentiation)of relatively uniform size.
- Depending upon the exact plane of section, the nests of a syringoma vary in shape, and some nests mayassume a morphology that resembles a **comma** or a **tadpole**
- The encompassing **stroma** is **sclerotic**

**Treatment**

- Syringoma is a benign adnexal neoplasm with negligible proliferative capacity. After definitive diagnosis, no further surgical intervention is needed
- Syringomas may be treated with careful application of **trichloroaceticacid, cryotherapy, punch excision, or electrosurgical destruction**
- This can be difficult with multiple lesions on eyelids
- Disseminated lesions canbe cosmetically disabling and therapeutically challenging, and laserablation might be the best choice

**QQ DD of syringoma ??**

# Fibrous tumors

## Skin tags
## (Acrochordons, Fibroepithelial polyps, Soft fibromas)

**Incidence:** very common (about 50% of all individuals have at least one skin tag)

**Clinical Features:**

- soft, skin-colored to slightly hyperpigmented, **pedunculated** papules
- common sites: **neck, axilla** and groin
- single or multiple
- vary in size from 1–2 mm (eyelids) to **1–2 cm baggy polyps (trunk).**
- usually **asymptomatic**, but can be **painful** (secondary to irritation or infarction مهم).

**Clinical DD:**

- intradermal melanocytic nevi
- neurofibromas
- pedunculated seborrheic keratoses.

**Epidemiology:**

- **Age:** incidence increases with age
- **Sex:** men and women are equally affected,
- **Associations:**
  - ***colonic polyps***
  - ***diabetes mellitus*** (skin tags have been reported as a cutaneous marker for DM)

**Pathology**

- Polypoid
- loose to dense collagenous stroma with thin-walled blood vessels
- overlying epidermis may be hyperpigmented and hyperplastic

**Adipocytes** are sometimes seen within **larger** skin tags (**lipofibroma**)

**Treatment**

Unless irritated or infarcted, skin tags are more of a **cosmetic** issue than a clinical concern and can be **removed** by **scissor excision.**

# Cutaneous angiofibroma

## Fibrous papule (of the nose), Pearly penile papule, Periungual fibroma

**Definition:**
a descriptive term for a **group** of lesions with **different clinical** presentations, but **similar histologic** findings.

**Clinical Features**

**(1) Fibrous papules (of the nose / face):**

- solitary, dome-shaped and shiny, skin-colored to reddish papules located on the **face** of **adults**, most commonly on the **nose**
- **Clinical DD:** small intradermal melanocytic nevi, basal cell carcinomas (BCCs) or adnexal tumors.
- **Removal** by shave excision and electrodesiccation.

**(2) Pearly penile papules:**

- pearly, white, dome-shaped, closely aggregated small papules located on the glans penis, commonly in a **multilayered and circumferential** manner on the **corona**
- found in up to **30%** of young **postpubertal adults**
- more common in **uncircumcised** men
- **clinical DD:** condyloma acuminata or hypertrophied sebaceous glands
- They are sometimes of significant **cosmetic** concern to the patient, but **no treatment** is needed, only **reassurance**.

**(3) Multiple facial angiofibromas:**

- seen in **tuberous sclerosis (TS = adenoma sebaceum)** مهم جداً, multiple endocrine neoplasia (MEN) type 1 and Birt–Hogg–Dubé syndrome
- distributed **bilaterally** on **cheeks, nasolabial folds, nose and chin.**
- Patients with **TS** can also have multiple **periungual angiofibromas (Koenen's tumors)**

**Pathology:**

- **All** angiofibromas are dome-shaped lesions composed of a dermal proliferation of **fibroblasts** in a collagenous stroma with an increase in the number of thin-walled, dilated **blood vessels**
- The **overlying epidermis** is sometimes slightly atrophic

# Dermatofibroma

## (Benign fibrous histiocytoma, Histiocytoma, Sclerosing hemangioma)

☆ the 2nd most common fibrohistiocytic tumor of the skin (after skin tags)

**Etiology:** precise etiology is not known

- arise at sites of **trauma** or **arthropod bites**
- Multiple eruptive dermatofibromas have been observed in patients with **autoimmune disorders** (e.g. lupus erythematosus), **atopic dermatitis** and in the setting of **immunosuppression** (e.g. HIV infection)

### Clinical Features

- seen primarily in **adults** and favor the **lower extremities**
- firm, dome-shaped papules (few millimeters to 1 cm in diameter)
- commonly **hyperpigmented** (in patients with lightly pigmented skin may appear tan to pink)
- On **palpation**, they may seem **attached to the subcutaneous tissue**; **pinching** the lesion gently usually results in apparent downward movement of the tumor, also known as the "**dimple sign**".

### Clinical DD

- Cysts, melanocytic nevi
- dermatofibrosarcoma protuberans (DFSP) مهم

### Pathology

- nodular dermal proliferation of **spindle-shaped fibroblasts**
- increased number of small **blood vessels**
- **hemorrhage** (sclerosing hemangioma) explains the common finding of hemosiderin
- perivascular infiltrate of **lymphocytes** and plasma cells
- The overlying **epidermis** is hyperplastic with flat confluent rete ridges and **hyperpigmentation of the basal layer** (so-called **"dirty fingers"**)
- مهم جدا جداً **Positive** immunohistochemical reactions for **factor XIIIa** and a **negative** reaction for **CD34**

### Treatment

☆ Dermatofibromas may be biopsied or **excised** to exclude a melanocytic proliferation, a fibrosed cyst or other mesenchymal neoplasm or for **cosmetic** purposes (??? the resultant scar is sometimes more noticeable than the original lesion, especially on the legs)

## Dermatofibrosarcoma protuberans (DFSP)

**Definition:** a locally aggressive **sarcoma** of intermediate malignancy

**Clinical Features**

- favors young to middle-aged **adults**
- occurs on the **trunk** (50–60%), the **proximal extremities** (20–30%), head and neck (10–15%)
- predilection for the **shoulder or pelvic region** مهم جدا.
- a slowly growing, asymptomatic, skin-colored, **indurated plaque** → violaceous to red–brown **nodules** (one to several centimeters in diameter)
- On palpation, the lesion is **firm** and **attached to the subcutaneous tissue (better felt than seen** مهم جدا).

**Clinical differential diagnosis:**

- keloid, large dermatofibroma, dermatomyofibroma and morphea

**Pathology**

- spindle-shaped cells arranged as short fascicles in a **"storiform" or mat-like** arrangement
- the cells **infiltrate the subcutaneous tissue** in a "**honeycomb**" pattern
- Nuclei are hyperchromatic, and mitotic figures are easily identified
- the spindle-shaped cells are strongly **positive for CD34** and **negative** for **factor XIIIa** مهم جداً

**Treatment**

**Complete surgical excision** is the standard treatment for DFSP
This tumor is characterized by its local invasion and tendency to recur

## Hypertrophic scars and keloids

**Both** are two forms of **abnormal wound healing** characterized by **local fibroblast proliferation** and **excessive collagen production** in response to **cutaneous injury**

- However, their clinical and histopathologic features differ, as well as proposed pathogeneses

### Epidemiology Keloid

☆ ***Race:*** higher incidence in **darkly pigmented** individuals of African ancestry

☆ ***Age:*** may occur at **any age** – more common between **10 and 30 years**

- **Younger** individuals are more frequently subjected to **trauma**
- Younger skin possesses **greater tension** (older skin is less elastic and has more redundancy)
- The rate of **collagen synthesis** is greater in younger persons

### Pathogenesis

***Keloid:***

Factors that play a major role in keloid development include…

1. **Genetic** predisposition +
   - ☆ a **familial tendency** to develop hypertrophic scars and keloids and possibly an **autosomal dominant** mode of inheritance
2. **skin injury** of any kind (e.g. lacerations, burns, surgical excisions, skin piercings and injections (vaccines, tattoo inks) +
3. cutaneous **inflammation** (e.g. acne vulgaris, insect bites) ⇨ role in ***spontaneous*** keloids ??????????

***Keloids and hypertrophic scars:***

1. **Wound or skin tension**
   - Loss of tissue as in a surgical excision ⇨ the attempt to close the wound creates tension
   - constant tension is transmitted to the skin from the underlying musculoskeletal structures
2. **Hormonal influences**
   - appearance of keloids at or after puberty and their resolution following menopause
   - reports of the onset or enlargement of keloids during pregnancy

3. **Abnormal wound healing:**
   - Normal wound healing occurs in **three** phases: the **inflammatory** phase, the **proliferative** or **granulation** phase, and the **maturation** or **remodeling**.
   - During the normal maturation phase, the nodularity and redness of the wound soften and flatten due to simultaneous collagen synthesis and degradation.
   - In keloids, collagen synthesis is ~20 times and 3 times greater than in normal non-injured skin and hypertrophic scars, respectively
   - This collagen overproduction is attributed to the activity of keloidal fibroblasts.
4. **Growth factors:**
   - transforming growth factor (TGF)-β
   - platelet-derived growth factor (PDGF)
5. **Other factors:**
   - Decreased production of molecules that promote matrix breakdown (e.g. matrix metalloproteinases [MMPs])
   - In comparison to normal dermal fibroblasts, keloidal fibroblasts exhibit a reduced rate of apoptosis

## Clinical Features

***Both keloids and hypertrophic scars***

- Have a smooth surface and are firm to palpation
- May be pruritic / painful - may inhibit normal motion of adjacent tissues
- The color can vary from pink–purple (early lesions) to skin-colored to hypo- or hyperpigmented
- favor sites of increased wound tension (e.g. upper trunk, deltoid region), but keloids can also appear in sites with minimal tension e.g. earlobe

| Keloids | Hypertrophic scars |
|---|---|
| ***More elevated*** above the skin surface than hypertrophic scars | |
| ☆ **The key difference:** ***Extend beyond*** the original wound margin into adjacent normal skin (claw-like extensions resembling the pincers of a crab) | Remain ***confined*** to the site of the original injury |

## Pathology

***Hypertrophic scars:***

- ☑ **increase** in both the number of **fibroblasts** (spindle-shaped) and density of **collagen** fibers within the dermis
  - the orientation of both the cells and the collagen becomes **parallel** to the skin surface
- ☑ dermal **blood vessels** are **vertically** oriented (i.e. perpendicular to the skin surface)
- ☑ **Elastic tissue** is **diminished** or absent
- ☑ ± a sparse perivascular inflammatory infiltrate

***Keloids:***

- ☑ **increased** number of **fibroblasts** and thick hyalinized **collagen** bundles in a **haphazard** array
  - **Early** ⇨ abundant deposits of **fibrillary** collagen within the **reticular** dermis
  - **Mature** keloids ⇨ strikingly **thick**, glassy, homogeneous collagen bundles (composed of multiple densely packed fibrils - oriented haphazardly throughout the dermis)
  - **Long-standing** keloids ⇨ there may be a **return** to the earlier **fibrillary** pattern
- ☑ the overlying **epidermis** and **papillary dermis** are uninvolved
- ☑ mucinous ground substance
- ☑ fewer, if any, **vertically oriented blood vessels** (compared with hypertrophic scars)

## Differential Diagnosis

1. **Distinguishing hypertrophic scars from keloids**
   - a keloid extends into adjacent tissue
   - a hypertrophic scar remains within the confines of the original injury

2. The sclerotic form of **xanthoma disseminatum**
   - may be confused with keloids clinically (but not histologically)

3. Keloidal forms of **scleroderma** and **morphea**

4. **Carcinoma en cuirasse** (may rarely present as keloidal nodules)

**Treatment** (The management of keloids and hypertrophic scars)
NO universally accepted treatment protocol

**Prevention** (the best strategy) - with predisposed patients ..

- avoiding non-essential surgery

**Treatment lines**

- ***Excision***
- ***Intra-lesional injection:***
  - ☆ Triamcinolone acetonide (10–40 mg/ml)
  - ☆ Interferon-α-2b
  - ☆ 5-Fluorouracil
  - ☆ Verapamil
- ***Physical:***
  - ☆ Laser (pulsed dye)
  - ☆ Radiation
  - ☆ Cryotherapy
  - ☆ Pressure
- ***Topical:***
  - ☆ imiquimod (5%)
  - ☆ tacrolimus
  - ☆ retinoids
- ***Silicone gel sheets***
  - ☑ Possible mechanism of action: increasing the temperature, hydration (reduces water vapor loss), and perhaps the oxygen tension of the occluded scar ⇨ decrease capillary activity ⇨ reduction in collagen deposition
  - ☑ This sheeting is also used as a preventative measure immediately after healing in patients at risk for developing hypertrophic scars or keloids.

☆ A combination of **surgery plus postoperative radiation therapy**
- ☑ immediately following excision – over a period of 2-3 consecutive days
- ☑ Radiotherapy-associated carcinomas?? (very low, especially when surrounding tissues are adequately shielded)

Intra-dermal injections of **avotermin** (recombinant human TGF-β3)
☆ TGF-β3 is a potential anti-scarring therapy

# Non-melanoma skin cancer (NMSC)

1. Basal cell carcinoma (BCC)
2. Squamous cell carcinoma (SCC)

## Risk factors for NMSC

| Environmental Exposures | Genetic Risk Factors |
|---|---|
| ***UV radiation***<br>• Sun exposure<br>• Therapeutic UV exposure e.g. long-term PUVA therapy<br>• Tanning lamp usage<br>***Ionizing radiation***<br>• X-ray therapy<br>***Occupational risk factors***<br>• Persons with outdoor occupations = UV exposure<br>• Airline pilots = ionizing radiation at flight altitudes<br>• Others e.g. agricultural workers, sailors, textile workers and locomotive engineers<br>***Chemical exposures***<br>• Pesticides, asphalt, tar and polycyclic aromatic hydrocarbons<br>• **Arsenic** (palmoplantar arsenical keratoses)<br>***Infections***<br>• Human papillomaviruses (HPV) infection = Epidermodysplasia verruciformis (EV)<br>• HIV infection e.g. SCC of the anus<br>***Other risk factors***<br>• Thermal burns, chronic ulcers and tobacco abuse<br>• Immunosuppression e.g. organ transplantation and Immunosuppressive drugs | ***Genetic predisposition***<br>Phenotypic characteristics e.g.<br>• light skin<br>• red hair<br>• poor ability to tan<br>• freckling<br>***Genetic syndromes associated with increased NMSC risk*** مهم جداً<br>• Xeroderma pigmentosum (XP)<br>• Oculocutaneous albinism<br>• Dystrophic epidermolysis bullosa<br>• Nevoid basal cell carcinoma syndrome (NBCC syndrome; Gorlin syndrome)<br>• Bazex syndrome<br>• Rombo syndrome |

## Treatment for NMSC

1. **Surgical excision**
   - BCC <2 cm in diameter = 4 mm margins
   - High-risk SCC requires 6 mm margins (size >2 cm, poor differentiation, invasion to fat,….)

2. **Curettage alone** For BCCs

3. **Curettage with electrodesiccation**
   - frequently used to treat BCCs
   - can be used for small SCCs in situ and well-differentiated primary SCCs <1 cm indiameter

4. **Mohs micrographic surgery**

5. **Radiation therapy**
   - used for treating BCC or SCC if surgery is contraindicated

6. **Cryosurgery**
7. **Photodynamic therapy**
8. **Laser** e.g. carbon dioxide laser

9. **Medical treatment**
   - Topical 5-fluorouracil = superficial BCCs
   - Topical diclofenac (NSAID)
   - Imiquimod cream
   - Intralesional injection of interferon- $\alpha$ -2b
   - Intralesional fluorouracil or methotrexate
   - **Hedgehog pathway inhibitors e.g. Vismodegib *******
     For BCC that cannot be treated with conventional therapeutic methods

# BASAL CELL CARCINOMA (BCC)

## Risk factors عادى

## Types 5 major clinico-pathologic types:

1. **Nodular**
   - While all types of BCC may ulcerate, ulceration is observed more often in the nodular type = **nodulo-ulcerative**
2. **Superficial**
3. **Morpheaform**
4. **Fibroepithelial (fibroepithelioma of Pinkus)**
5. **Pigmented**

## Clinical Features

### (1) Nodular BCC

- the **most common** subtype (**50%** of all BCCs)
- shiny, pearly **papule or nodule** with a smooth surface and **telangiectasia**
- the tumor may enlarge and **ulcerate** (**rodent ulcer**, phagedenic ulcer) with an **elevated rolled border** (a clinical **clue** to the diagnosis)
- **Sites**: **face**, especially the cheeks, nasolabial folds, forehead and eyelids (may arise in any hair-bearing area of the skin)

### (2) Superficial BCC

- well-circumscribed, erythematous, macule/**patch** or thin papule/plaque (diameter varying from a few millimeters to several centimeters)
- + focal scale and/or crusts, a **thin rolled border**
- in larger lesions, areas of spontaneous **regression** may be present, characterized by atrophy and hypopigmentation.
- PRESENT AT a **younger** age than for other types of BCC
- favors the **trunk** and extremities (less often in the head and neck region)

### (3) Morpheaform BCC

- less common subtype
- a slightly elevated to even depressed **area of induration**, light pink to white in color with **ill-defined borders** (resembles a scar or plaque of morphea)

- elevated pearly border is typically absent (BUT telangiectasias may be present)
- The biologic behavior is usually more **aggressive**, with **extensive local destruction**.

**(4) Fibroepithelial BCC**
- **rare** variant
- a skin-colored or pink, **sessile plaque** or **pedunculated** papulonodule with a smooth surface
- favors the **trunk**, especially the **lower back**

**(5) Pigmented BCC**
- observed more commonly in those with **darker skin phototypes**
- **NB.** the majority of BCCs are amelanotic – variable amounts of melanin may be present

## Differential diagnosis

**(1) Nodular BCC**
- ***non-ulcerated lesions:***
  - intradermal melanocytic nevi (softer) أول هام
  - adnexal neoplasms تانى هام
  - Merkel cell carcinoma
  - Melanoma (amelanotic more often than melanotic)
- ***Ulcerated lesions***

Ulcerative lesions commonly affecting face e.g. leishmaniasis, traumatic ulcers, lupus vulgaris ….

**(2) Superficial BCC**
- **Bowen's** disease
- Inflammatory diseases e.g. psoriasis, **dermatitis** and cutaneous lupus erythematosus
- **Paget's** disease

**(4) Fibroepithelial BCC**
- a large fibroepithelial polyp (skin tag)
- intradermal nevus.

## Histopathology

All types of BCC have a common histopathological picture of ..

- **masses** of **basaloid** cells (keratinocytes) surrounded by **fibromyxoid stroma**
  - cell masses show a **peripheral palisading**
  - A characteristic feature of BCC is **retraction of the stroma** around the tumor islands, creating microscopically visible **clefts**

- In **nodular** BCC ⇨ large, round or oval aggregations (classic)

- **Superficial** BCCs ⇨ small, superficially located buds of basaloid cells extending no more deeply than the papillary dermis

- **Pigmented** BCCs ⇨ contain aggregates of melanin, melanocytes and melanophages

- **Morpheaform**, sclerosing and infiltrative BCCs ⇨ strands and cords of basaloid keratinocytes extending between collagen bundles + absent peripheral palisaded pattern and stromal retraction (cleft formation)

- **Fibroepithelioma** of Pinkus ⇨ thin anastomosing strands and cords of tumor cells that project downward from the epidermis in a fenestrated pattern and are embedded in a fibrous stroma

**Additional histopathologic subtypes of BCC**

- **Micronodular** BCCs are composed of tumor islands much smaller than those of nodular BCC

- **Basosquamous** carcinoma (**metatypical** BCC) is a tumor that has histologic features of both BCC and SCC. These tumors may behave biologically more like a SCC than a BCC, i.e. have more aggressive behavior with a greater likelihood of recurring after treatment and metastasizing

## Treatment of BCC عادى

## Syndromes in which *multiple* BCC occur (5)

**(1) Nevoid basal cell carcinoma syndrome (NBCC syndrome; Gorlin syndrome)**

- rare, AD disorder
- due to a mutation in the human PTCH
- clinical features:
- **multiple or early-onset BCCs**, odontogenic keratocysts of the jaw, palmoplantar pits, calcification of the falx cerebri, and skeletal anomalies

**(2) Bazex syndrome**

- rare condition
- X-linked dominant
- follicular atrophoderma (usually occurring as circumscribed areas on the dorsal aspect of the hands and feet), hypotrichosis, localized hypohidrosis, milia, epidermoid cysts, and **multiple, primarily facial, BCCs**

**Bazex syndrome (acrokeratosis paraneoplastica)** = psoriasiform plaques of the fingers, toes, ears and nose + SCC of the upper aerodigestive tract
حاجه تانيه

**(3) Rombo syndrome**

- multiple BCCs
- atrophoderma vermiculatum-like appearance on the cheeks
- hypotrichosis, blepharitis, peripheral (facial/acral) telangiectatic erythema, milia, trichoepitheliomas

**(4) Xeroderma pigmentosum (XP)**

- AR
- defects in DNA repair mechanism
- A markedly increased incidence of NMSC and melanoma
- NMSCs appear at an early age (median age, 8 years)

**(5) Linear unilateral basal cell nevus**

- Rare
- Unilateral linear extensive BCC nodules + comedones + linear atrophy

# Squamous cell carcinoma (SCC)

## Risk factors: عادى

## Clinical features:

- SCC usually arises within a **sun-damaged skin**, most commonly on the **bald scalp**, face, neck, extensor forearms, dorsal hands and shins
- The color varies from **erythematous** to skin-colored (rarely pigmented)
- SCCs are often **papulo-nodular**, but can be plaque-like, papillomatous or exophytic
- The degree of associated **scale** varies, with some lesions becoming **hyperkeratotic**
- **Secondary changes** include crusting, erosions and ulcerations

## Verrucous carcinoma مهم جداً

- Verrucous carcinoma is a **rare**, **well-differentiated** variant of SCC i.e. a **low-grade malignancy**

- **Three** major subtypes:
  (1) epithelioma cuniculatum (plantar surface of the foot)
  (2) giant condyloma acuminatum of the genitalia (also known as Buschke–Lowenstein tumor)
  (3) oral florid papillomatosis (oral mucosa)

- Clinically ⇨ **large** (sometimes **huge**), exophytic tumors with a papillomatous or verrucous surface
- **Gradual** penetration of verrucous carcinomas into underlying tissues can result in destruction of subcutis, fascia and bone

- They are commonly associated with **HPV infection**
- These tumors can arise within **scars** and **amputation stumps** and in association with osteomyelitis fistulae and chronic venous insufficiency

- Verrucous carcinomas often **recur** after surgical removal, but they usually **do not metastasize,**

## Histopathology

- Masses of cells (glassy, brightly eosinophilic = keratinocytes) present within the dermis at varying levels and containing nuclei with some degree of pleomorphism and mitoses
- The pink colour of the cytoplasm arises from abundant high-molecular-weight keratin
- Horn pearls = eosinophilic parakeratotic keratinization

## Treatment عادى